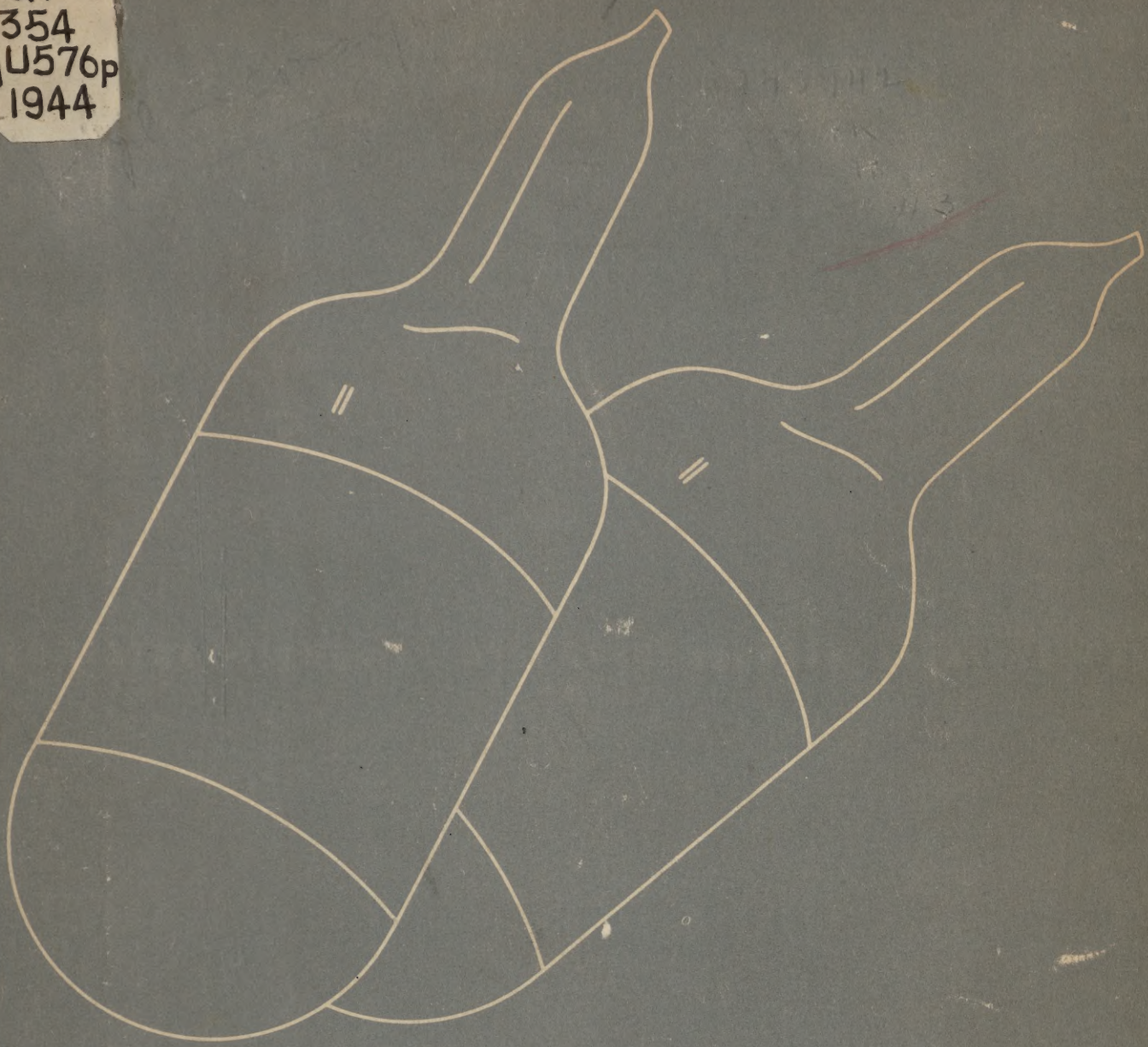

PENICILLIN

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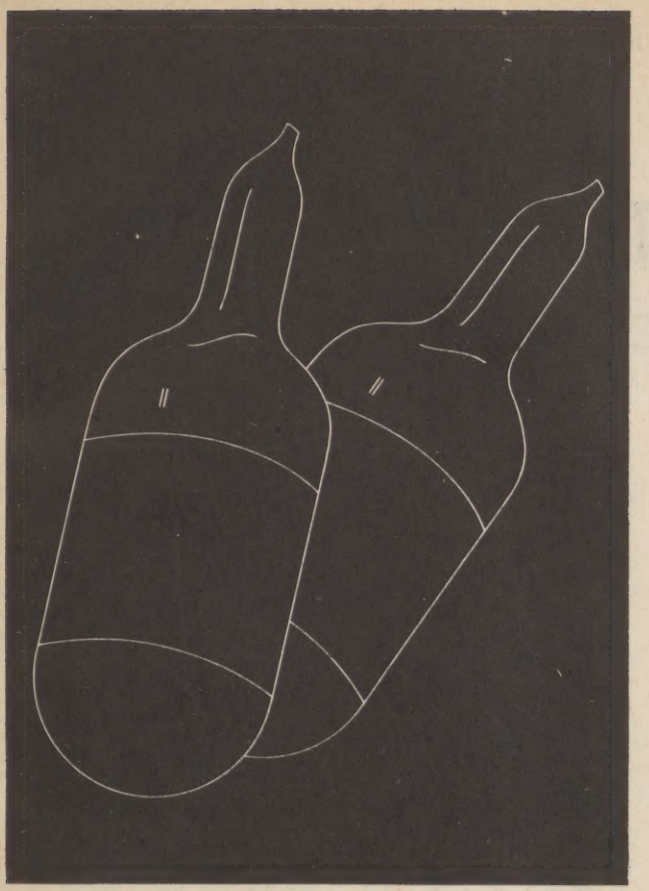
1944



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PENICILLIN

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THE HISTORY OF PENICILLIN

Recently the *British Medical Journal* said editorially [1] that the history of penicillin is essentially the story of three distinct developments: "The first was Fleming's discovery; [2] the second was the victory of Florey and his colleagues, who showed how to obtain penicillin in a relatively pure form and who demonstrated its clinical use"; [3] the third "victory," the editor generously points out, lies in the American success in large scale

production of the drug. Sir Howard Florey[4] in the same issue of the *British Medical Journal* gives a detailed survey of the development of penicillin studies. He mentions that in 1877, prior to Fleming's disclosure, Pasteur and Joubert[5] had observed that cultures of anthrax ceased to grow when contaminated with air bacteria; this, Florey believes, was the first evidence that a substance produced by one organism is capable of arresting the growth of another. In the years that followed, many other "antibiotics" were discovered; one, an extract from Bacillus pyocyaneus, was placed on sale in Germany in 1930 as an unguent for local application to the skin lesions arising from anthrax.[6]

After noting conspicuous inhibition of growth in a colony of staphylococcus contaminated by mold, Fleming subcultured the mold in broth and found that a strong antibiotic, nontoxic to animals, passed into the broth from the mold;[2] the mold was later identified by Thom in this country as Penicillium notatum, and Fleming designated the antibiotic agent "penicillin." He found that penicillin inhibited the test tube growth of many gram positive bacteria known to be highly pathogenic to man; he also noticed that his penicillin-containing broth did not disturb white blood cells; on applying the solution to several clinical cases of local skin infection he reported[4] that the results "appeared to be superior to dressings containing potent chemicals." Several years later Clutterbuck, Lovell and Raistrick,[7] stimulated by Fleming's study, attempted to extract penicillin, but their efforts were largely unsuccessful; they concluded that the penicillin was too "labile" to be of clinical use. In this conclusion Sir Alexander Fleming reluctantly concurred. If one may judge by his published work, Fleming then abandoned further study of the agent until 1941,[8] except as he used it for differential culture.[9]

The successful isolation of penicillin, the clearcut proof of its clinical usefulness, its assay and dosage, as well as the mode of its excretion from the body are credited to Howard Florey and his resourceful associates at Oxford. In 1929, the year of Fleming's first paper, Florey began work on lysozyme,[10] an antibiotic discovered by Fleming in 1922 and ultimately crystallized by Roberts in 1937.[11] During the next ten years Florey continued his study of various antibiotics, firm in the conviction that one nontoxic to human beings would be found which would be of value in treating human infections. The discovery of the clinical effectiveness of penicillin was thus an outcome of a broadly conceived program of study and not an advance immediately associated with the war. Ultimately the war immeasurably expedited the development of penicillin, but during the early stages of the work wartime restrictions considerably impeded the study; for, once it had been disclosed how penicillin might be successfully extracted, it proved impossible in England (in 1940) to initiate large scale production.

Florey first directed his attention to penicillin in 1938, when he was joined by an able continental biochemist, Dr. E. Chain; between them a plan was laid for a systematic study of penicillin and other naturally occurring antibacterial agents. Drs. Florey and Chain were presently joined by Drs. E. P. Abraham, A. D. Gardner, Norman G. Heatley, M. A. Jennings, J. Orr-Ewing, A. G. Sanders, C. M. Fletcher and also by Lady Florey, a physician of competence who has been largely responsible for studying the effectiveness of penicillin applied to locally infected areas. The ultimate success of the research largely depended on the development of a reliable procedure for assay. The test adopted was worked out by the microchemist of the team, Dr. Norman Heatley, and consisted in determination of the rate of inhibition of growth of a standard bacterial culture. Through the use of an ingenious extraction method involving the passing of impure acid penicillin broth from a watery solution into an organic solvent (ether or amyl acetate) and the subsequent passing of the purified agent again into water (shaken with alkali), they obtained sufficient penicillin for clinical trial. The first patient was treated on Feb. 12, 1941; the response was dramatic, but the supply of penicillin ran out and shortly thereafter the patient had a relapse and died. As might have been expected, the Oxford team encountered difficulty in obtaining suitable cases for clinical trial, and patients eventually turned over to them were generally moribund with advanced septicemia. By June 1941 6 such patients had been treated intravenously; all had responded, but 2 had died when the penicillin supply became exhausted.[12]

Undeterred by difficulties and an apathy that would have caused many to abandon the work until after the war, Florey, accompanied by Dr. Heatley, came to this country in July 1941 under the auspices of the Rockefeller Foundation, requesting that the National Research Council in Washington lend a hand in the medical study of penicillin, and more particularly in the attack on the problem of production. Through the foresight of Ross G. Harrison, chairman of the National Research

1. Brit. M. J. **2**: 186 (Aug. 5) 1944; Brit. M. Bull. **2**: 4 (Jan.) 1944.
2. Brit. J. Exper. Path. **10**: 226 (June) 1929.
3. Lancet. **2**: 226 (Aug. 24) 1940.
4. Brit. M. J. **2**: 169 (Aug. 5) 1944.
5. Compt. rend. Acad. d. Sc. **85**: 101, 1877.
6. Ztschr. f. Hyg. u. Infektionskr. **31**: 1, 1899.
7. Biochem. J. **26**: 1907 (Nov.) 1932.
8. Nature, London **148**: 757, 1941.
9. Fleming writes "I have used penicillin constantly since 1929 for differential culture but its use for practical therapeutic purposes remained in abeyance until the Oxford workers started their investigation" (Brit. M. Bull. **2**: 5 [Jan.] 1944).
10. Brit. J. Exper. Path. **11**: 251 (Aug.) 1930.
11. Quart. J. Exper. Physiol. **27**: 89, 1937.

Council, Florey was put in touch at once with the fungus laboratories of the Department of Agriculture, and through the cooperation of Dr. Coghill, director of the Fermentation Division of the Department of Agriculture's research laboratory at Peoria new methods were worked out for increasing yield; within a few months large scale production of penicillin was begun by a group of enterprising American drug houses. The earliest patient to be studied in this country under the auspices of the Office of Scientific Research and Development was first treated with penicillin on March 14, 1942 in New Haven, Conn., an advanced case of hemolytic streptococcus septicemia, which responded most dramatically to the drug.[13]

Dr. Florey had returned to England in September 1941. Dr. Heatley remained in this country for some twelve months to assist in the negotiations for the large scale production of the drug; during this time Heatley rendered invaluable assistance in supervising assay of the early yields. Professor Florey devoted the following year (1942) to studying ways of purifying penicillin and, in association with Lady Florey, conducted a highly significant investigation on local application of penicillin; since supplies were still low there was too little available for general administration.[14] In the summer of 1943 Florey and Brigadier Hugh Cairns, consulting neurosurgeon to the Royal Army Medical Corps, were sent to North Africa by the British War Office to study the uses of penicillin in war wounds. They returned three months later with a radical report which insisted [15] that open flesh wounds and wounds of the head can be safely and tightly closed if dealt with early, provided penicillin solution is administered locally in the wound after thorough débridement. Their initial experience has been strongly vindicated during the past year by other British medical officers as well as by medical officers of our own Army and Navy. To quote a conservative report,[16] "The percentage of scalp and brain wounds that heal by primary union has always been a high one when operation is performed at special neurosurgical units. In Italy, with greater infectivity of the terrain, this standard tended to deteriorate whenever penicillin was in short supply but was maintained when penicillin-sulfathiazole powder was insufflated to surface wounds and into depths of brain." Less conservative, but not less significant, is Florey and Cairns' original statement [15] that of 171 recent (three to twelve days) soft tissue wounds 104 closed by primary union, 60 closed with some degree of granulation and 7 were classified as failures. "None of the patients," they add, "in this series has been placed in danger [i. e. there were no fatalities]. This is a remarkable fact when we consider that the wounds closed included large and purulent wounds of the worst type—for example, large buttock wounds infected with hemolytic streptococci and clostridia. Only once was it necessary to release the stitches; this was in a penetrating chest wound and cellulitis of the chest wall. . . . Cases with complete union (104) call for no comment. In cases with subtotal union (60) the gaping area usually healed rapidly by granulation. The failures (7) occurred in the early stages of the investigation and could usually be attributed to errors in technique of skin closure and rarely to persistence of pyogenic cocci. These patients came to no harm, and the attempt at closure did not interfere with their healing by granulation." A wound which heals by primary intention requires three weeks; if granulation occurs, six to twelve weeks may elapse. The military significance of this is too obvious to require comment. Indeed, many have come to feel that penicillin will transform our entire concept of management of wartime injuries, and it will no doubt have a similarly far reaching effect on civilian traumatic surgery.

Sir Howard Florey had scarcely returned from North Africa when he was summoned early in 1944 to Moscow, where he was able to give our Soviet allies first hand information concerning penicillin, particularly with regard to local administration in war wounds; on his return from the Soviet Union, Australia, the country of his birth, requested his counsel.

The *British Medical Journal* gives deserved and generous credit to Dr. A. N. Richards, chairman of the Committee on Medical Research, and to the Office of Scientific Research and Development for sponsoring the medical aspects of the penicillin program in this country. One can only add that part of Dr. Richards' wise direction of the program lay in his fortunate selection of the Division of Medical Sciences of the National Research Council working through the Committee on Chemotherapeutic and Other Agents with its succession of able chairmen (Col. Perrin Long until July 1942 and thereafter Dr. Chester S. Keefer) as the official body responsible for supervising and directing both the formidable production schedule and the various research projects, two of the most significant of which were reported upon in last week's number of THE JOURNAL. The story of penicillin will long exemplify the highest traditions of medical research and, incidentally, the rich fruits of a sound international cooperation in wartime.

12. Lancet **2**: 177 (Aug. 16) 1941.
13. Tr. A. Am. Physicians, to be published; Yale J. Biol. & Med. **15**: 507 (Jan.) 1943.
14. Lancet **1**: 387 (March 27) 1943.
15. Florey, H. W., and Cairns, Hugh: A Preliminary Report to the War Office and the Medical Research Council on Investigation Concerning the Use of Penicillin in War Wounds [London], War Office (A. M. D. 7), October 1943.
16. Brit. M. J. **2**: 1 (July 1) 1944.

At periodic intervals the Council on Pharmacy and Chemistry will offer brief statements on the present status of therapeutic or prophylactic procedure in fields of current interest. This information will be selected for its special value to those engaged in general practice.

Austin E. Smith, M.D., Secretary.

PENICILLIN

EFFECTIVE IN

All *staphylococcic infections* with and without bacteremia:
- Acute osteomyelitis
- Carbuncles—soft tissue abscesses
- Meningitis
- Cavernous or lateral sinus thrombosis
- Pneumonia—empyema
- Carbuncle of kidney
- Wound infections

All cases of *clostridial infections:*
- Gas gangrene
- Malignant edema

All *hemolytic streptococcic infections* with bacteremia and all serious local infections:
- Cellulitis
- Mastoiditis with intracranial complications, i. e. meningitis, sinus thrombosis, etc.
- Pneumonia and empyema
- Puerperal sepsis
- Peritonitis

All *anaerobic streptococcic infections:*
- Puerperal sepsis

All *pneumococcic infections* of
- Meninges
- Pleura
- Endocardium

All cases of sulfonamide resistant pneumococcic pneumonia

All gonococcic infections complicated by
- Arthritis
- Ophthalmia
- Endocarditis
- Peritonitis
- Epididymitis

Also all cases of sulfonamide resistant gonorrhea

All meningococcic infections not responding to the sulfonamides

NOT ESTABLISHED AS EFFECTIVE FOR

All gram-negative bacillary infections:
- Typhoid—Paratyphoid
- Dysentery
- Escherichia coli
- Haemophilus influenzae
- Proteus vulgaris
- Bacillus pyocyaneus
- Brucella melitensis (undulant fever)
- Tularemia
- Friedländer's bacillus

Tuberculosis

Toxoplasmosis

Histoplasmosis

Acute rheumatic fever

Lupus erythematosis disseminatus

Infectious mononucleosis

Pemphigus

Hodgkin's disease

Acute and chronic leukemia

Ulcerative colitis

Coccidioidomycosis

Malaria

Poliomyelitis

Blastomycosis

Nonspecific iritis and uveitis

Moniliasis

ADMINISTRATION

Method of Preparing Penicillin for Treatment

Penicillin is supplied in ampuls of different sizes—25,000 units and 100,000 units each. As penicillin is extremely soluble, it may be dissolved in small amounts of sterile distilled, pyrogen-free water or in sterile isotonic solution of sodium chloride. When large unit sizes are being used in hospitals, the contents of the ampul should be dissolved in water or saline solution so that the final concentration is 5,000 units per cubic centimeter. This solution should be stored under aseptic precautions in the ice box and made up fresh every day. Solutions for local or parenteral use may be diluted further, depending on the concentration desired.

For intravenous injection

1. The dry powder may be dissolved in sterile isotonic solution of sodium chloride in concentrations of 1,000 to 5,000 units per cubic centimeter for direct injection through a syringe.

2. The dry powder may be dissolved in sterile saline or 5 per cent dextrose solution in lower dilution (25 to 50 units per cubic centimeter) for constant intravenous therapy.

For intramuscular injection

1. The total volume of individual injections should be small, i. e. 5,000 units per cubic centimeter of isotonic saline solution.

For topical application

1. The powdered form of the sodium salt is irritating to wound surfaces and should not be used.

2. Solutions in isotonic salt solution with a concentration of 250 units per cubic centimeter are satisfactory. For resistant or more intense infections this concentration may be increased to 500 units per cubic centimeter.

DOSAGE

The dosage of penicillin will vary from one patient to another, depending on the type and severity of infection. Recovery has followed in many serious infections following 40,000 to 50,000 Oxford units a day; in others 100,000 to 120,000 or even more is necessary. The objective in every case is to bring the infection under control as quickly as possible. It is well to remember that penicillin is excreted rapidly in the urine, so that following a single injection it is often impossible to detect it in the blood for a period longer than two to four hours. It is well, therefore, to use repeated intramuscular or intravenous injections every three or four hours or to administer it as a continuous infusion.

In the treatment of *meningitis, empyema* and *surface burns of limited extent,* penicillin should be injected directly into the subarachnoid space, into the pleural cavity, or applied locally in solution containing 250 units per cubic centimeter.

3

Penicillin-

MICROBIOTIC CHEMOTHERAPY

19

The recent emphasis upon the new extract derived from media upon which Penicillium notatum has been cultured, prompted by its now proven chemotherapeutic value, brings to pharmacists and physicians an improved potent agent which will supplement and perhaps supplant the sulfonamides.

PREVIOUSLY, in the literature,[1] material has appeared from time to time on the new mycologic chemotherapeutic agent, penicillin. However, in the past few months considerable progress has been made with the therapeutic use of this compound, and a greatly increased medical and scientific awareness of its value has developed.

Discovery

It is interesting to note that the bacteriostatic activity of a principle in the mold was discovered entirely by accident. In a bacteriological laboratory in England, some four years ago, a worker neglected to place in the refrigerator certain inoculated media dishes. A mold formed which was identified routinely as a common type, *Penicillium notatum*. Out of curiosity one of the assistants observed the mold on the media under the microscope. He found an area surrounding the mold which was clear of bacteria, and when other organisms were moved into that sphere, they too were killed. Thus, as a result of an accident, penicillin was discovered.[1]

Penicillin had been originally studied[2] in 1929 by Fleming.[3] It was investigated insofar as was possible at the time by others.[10] It has been used for differential culture purposes bacteriologically. Finally Chain and his coworkers, in 1940, reported for the first time[4] an evaluation of its therapeutic effect and of its low toxicity, following the work of Dubos on soil bacillus antibacterial substances.

Activity

Fundamentally, penicillin is believed active against a number of organisms, particularly those gram-positive, the staphylococci and gonococci, especially those which exhibit sulfonamide-resistant properties. Reference should be made later in this paper and to a preceding article of this series,[1] for additional data.

Penicillin is not related to, nor does it behave like any of the chemotherapeutic substances now in use.[3] It is not hemolytic, and it is highly soluble. It is not a detergent and is not inhibited by para-aminobenzoic acid nor by the products of tissue destruction. It may be a complex member of the large aromatic or coal-tar group of compounds, and may in the future be synthesized from such derivatives. Some conjecture has been made that the formula may be $C_{14}H_{19}NO_6$ or $C_{14}H_{17}NO_5+H_2O$, with the nitrogen in question.

Heilman and Herrell began the investigation of the anti-bacterial activity of penicillin early in 1941 and confirmed[6, 7, 8], with a few minor differences, the observations made by the original investigators at Oxford.[4, 9] Hobby and her associates further confirmed these findings.[11, 12, 13]

Excellent Clinical Results

The reports which have been made available to date even under the restrictions of war-time control have borne out still further the excellent results obtained under the clinical trial of this new chemotherapeutic agent. However, inasmuch as only limited quantities of penicillin have been available up to this time, reports have been fragmentary and not as thoroughly controlled as would be the case with a drug in ample supply. Most workers caution against its indiscriminate use, for this reason.

Gram-negative Infections

Herrell and his associates[14] at the Mayo Clinic reported gratifying results in December of last year (1942), on the clinical use of the drug. They indicate, however, that penicillin is not of value in treating infections caused by the more common

gram-negative organisms, or against green-producing streptococci such as *S. faecalis*. Thus far it has shown no effect against *Mycobacterium tuberculosis*. It is not indicated in subacute bacterial endocarditis, as only occasional strains of the etiologic streptococci are affected by the action of penicillin. The drug may temporarily free the bloodstream of such organisms, but the valvular lesion which is involved continues. In such cases it has been found that the streptococci which are affected appear again in the bloodstream within four to six hours after the drug is discontinued. *B. proteus* and *pseudomonas* (*pyocyaneus*) tend to persist also, after therapy.

Gram-positive Organisms

For infections in which the etiologic agents are *Staphylococcus aureus, Streptococcus pyogenes,* susceptible strains of *Diplococcus pneumoniae, Neisseria gonorrhaeae* and *Neisseria intracellularis* it is exceedingly useful. Various experiments have led to the theory that it should be of value in treating the infections attendant upon gas gangrene caused by *Clostridium welchii.* Clinical trials against *Actinomyces bovis* are under way at present. Herrell *et al* employed penicillin in treating a case of severe facial and orbital cellulitis due to *S. aureus,* complicated by septicemia, and the patient recovered.

Robinson[15] showed that based upon weight, penicillin revealed more effect than did sulfanilamide and its derivatives in streptococcal pneumococcal and staphylococcal infections in mice. The above experimental work also showed that the drug had no noticeable effect in experimental infections caused by *Mycobacterium tuberculosis, Trypanosoma equiperdum* or the influenza virus PR8.

Pus-causing Bacteria

Other workers have also shown that penicillin is highly effective against those organisms such as the pus-causing bacteria. The sulfonamides are only moderately effective against these organisms. Many minor infections, such as pimples and boils, are caused by these common inhabitants of the skin surface. Serious infections complicating burns and wounds are also often traceable to these organisms. Osteomyelitis is likewise caused by these organisms. It should be noted that 90 percent of all war wounds show presence of staphylococcus infections.

Mold cultures grow in bottles. The most efficient strain had to be selected and matched with an efficient nutrient, and then harvested at peak development. Extraction from media is a solvent process at low temperature with a high vacuum.

Staphylococci

In previous wars, the infections caused by the staphylococci have been the major causative agents of death and disability. In a number of recent cases of staphylococcal infection of the blood, sulfonamides were first administered to no avail due to organism resistance. When penicillin was given, the cases were quickly improved and eventually discharged as cured. In fact penicillin is the only drug known at present for effective use in advanced cases of staphylococcic septicemia. One of its chief values is that of effectiveness in presence of serum or exudates. Against localized and systemic infections penicillin retains its activity *in vivo.* Penicillin causes a temperature drop but over a much longer period of time than do the sulfonamides.

Burns

Penicillin was successfully employed in the treatment of many casualties in the "Cocoanut Grove fire" in Boston. Each such case at the Massachusetts General Hospital was routinely given sulfadiazine, to prevent a streptococcus infection from beginning on the burned areas. If an in-

creased temperature was still present after six days, 5,000 units of penicillin were administered intramuscularly every four hours to counter a staphylococcic infection. None of these patients died of staphylococcic poisoning.[17]

Miscellaneous Uses

Penicillin also differs from the sulfonamides, in that it frequently increases the appetite, and anemia, if present, may show improvement.

Florey has advised its use in surgical operations of certain types. In 22 cases of mastoid operations, when completed he immediately stitched the incisions and provided a small rubber tube running to the bottom of the wound and in turn closed with a stopcock. At intervals of six hours the tube was drained and filled with a solution of penicillin. The tube was removed after a week's time. Only three of the 22 cases required further treatment to complete healing.

Drains were employed in the treatment of old wounds. The sinuses were filled with the solution and closed with a rubber stopper. The solution was changed twice daily. There were 11 cases with wounds which had existed for three months to 12 years, to which the treatment was given. Seven of the 11 healed within four weeks.

Streptococcal Meningitis

One case[20] of streptococcal meningitis has been reported, in which sulfapyridine and sulfathiazole were of little value. Penicillin was injected for eight days. Administered every two hours for the first 24 hours, it was then given every day following at two hour intervals from 8:00 a.m. to 8:00 p.m. with a dose of 10,000 units at 10:00 p.m. It was administered intramuscularly, and for five doses intrathecally. After an apparently hopeless prognosis, the condition improved on treatment and the progress made was excellent, with the temperature remaining at 98.6° F. after seven days.

Another report from England[21] stated that penicillin, when injected at the site of the infection, acted within three hours as a powerful prophylactic and in this respect is superior to proflavine and the sulfonamides.

Osteomyelitis

Chronic osteomyelitis, unhealed compound bone fractures with wounds accompanied by long established infections, are common in war casualties. Penicillin is particularly effective in both acute and after six days, 5,000 units of penicillin were administered intramuscularly every four hours to counter a staphylococcic infection. None of these patients died of such conditions. Some of these cases had been under treatment for months, unsuccessfully, with retarded healing and heavy suppurative lesions. Local administration in open wounds was effective even without accompanying systemic treatment, although the latter is routinely employed. Due to encouraging results the clinical use is being extended to ten general Army hospitals, to venereal disease investigations in six institutions, and somewhat less extensively to use in the Navy.[21]

Gonorrheal Infections

Herrell and his associates[18] more recently reported on the study of penicillin against several strains of *Neisseria gonorrheae* isolated from patients in whom the infection was completely resistant to "sulfa-drug" therapy. Even in fairly high dilutions of an active form of penicillin, these organisms were inhibited. The number of organisms was greatly reduced after one to two hours contact in bacterial cultures. No viable organisms could be found in the period between the second and third, or third and fourth hours. Chronic gonorrhea can usually be cured by sulfonamides in a period of about ten days but hospitalization for much longer periods is necessary in sulfonamide resistant cases. Penicillin has shown complete recovery of even the latter cases in from 24 to 72 hours. In heavy blood stream infections, when beginning therapy,[19] doses as large as 15,000 units every three hours should be given. This avoids a resistance which bacteria can develop to the drug in lower concentrations.

Toxicity

In addition, penicillin gives no evidence of toxicity when the product is pyrogen-free. It gives no discomfort to the patient; and in some cases causes rapid disappearance of clinical symptoms. In all of the cases studied by these workers, negative bacterial cultures were obtained in from 17 to 48 hours after the initial dose.

Penicillin lacks any apparent toxicity in humans, which is an advantage over the sulfonamides, as the latter frequently produce reactions. Crude penicillin was found[15] to be toxic for mice when adminis-

tered intravenously in single doses of 0.5, 1.0, 1.5 and 2.0 Gm., per Kgm. of body weight. The more highly purified products were less toxic.

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17. *Time 41*:41 (1943) #6.
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20. *Lancet* (1943) Mar. 27.
21. *Lancet 2*:745 (1942) Dec. 26.

Penicillin-

Continuing the discussion of this interesting new mycologic chemotherapeutic agent, which promises to replace sulfonamides in medical practice when adequate supplies are available, the physician is told of the culture and extraction, and the administration of penicillin.

IN the preceding article of this series, presented in last month's issue of this journal, the history, pharmacology and standardization of penicillin were discussed. Of approximately equal therapeutic value to the sulfonamides in all conditions in which clinical trial has been affected, penicillin has proven of use in "sulfonamide-resistant" cases of acute and chronic osteomyelitis, chronic gonorrhea, as well as in numerous other critical conditions.

When administered subcutaneously daily in doses of 1.6 Gm. per Kgm. for five days the penicillin was well tolerated. A dose of 3.2 Gm. per Kgm. daily has been found lethal to some mice. However, the toxic dose of the crude penicillin is approximately 64 times the effective dose for subcutaneous administration to mice.

Penicillin's effect is great upon metabolic burden of tissue repair; depletion of plasma protein and wide fluctuation in fluid balance, in wound cases, were noted.

Penicillin is eliminated rather rapidly in the urine. It is necessary to continually check the concentration in the wound or bloodstream so that there is sufficient penicillin present as long as it is needed.

As penicillin is not at present produced in large quantities, it is advantageous that it is so effective in high dilution. Similar to the sulfonamide drugs it has the advantage over antiseptics such as silver nitrate, bichloride of mercury and iodine that in the local application it penetrates the tissues to the location of the bacterial activity. It does not injure normal processes of the body. An added advantage over the "sulfa drugs" is that penicillin is not inhibited by pus or other body fluids.

In the blood stream penicillin acts as a bacteriostatic agent, that is, it prevents bacteria from multiplying and renders them susceptible to the action of the white corpuscles.

Herrell[5] states that penicillin in solution which is not pyrogen-free, may be administered locally in treating infections due to susceptible organisms. However, there are more available germicides of similar antibacterial activity. In oral administration it gives only fair results and must be protected against the acid phase of the stomach, which renders the substance impotent. Subcutaneously, a nonpyrogen-free material may be used in small amounts. It is also administered intramuscularly. It can be administered locally in powder or ointment form, with frequent application desirable.

Continuous Intravenous Therapy

Herrel recommends as most suitable the continuous or nearly continuous intra-

venous administration of the pyrogen-free solution of penicillin. This insures a more uniform and continued contact between the antibacterial agent and the bacteria invading the blood stream. Penicillin has been shown to produce a resistance in organisms if increasingly larger amounts are administered or if organisms are cultured and transplanted in media containing increasing amounts of the drug. Periodic injections for therapy may do much to encourage the growth of penicillin-resistant organisms.

Administration

In the therapy[15] of moderately severe or severe infections 30,000 to 40,000 Oxford units every 24 hours are sufficient. One-half of the dose is dissolved in one liter of physiological solution of sodium chloride, or in a five per cent solution of glucose in triple distilled water. The first 100 to 200 cc. are administered intravenously at a fairly rapid rate, which is then reduced to 30 to 40 drops per minute. Eight to ten hours later, the second liter should be started. When the penicillin is not being administered, glucose solution can be allowed to drop in slowly, to avoid repeated venipunctures. The arm is kept in rigid position by means of a simple arm splint.[9]

If an intermittent technic is desired the concentrate may be dissolved in 10 cc. or more of pyrogen-free distilled water. It is then administered intravenously or intramuscularly in doses of 20,000 units of penicillin every two hours.

Duration

Penicillin must be administered until the temperature is restored to normal, and until blood cultures are negative. Doses may be reduced, but administration should not be stopped entirely until the patient shows improved resistance to the infection.

Mechanism of Action

McIlwain[22, 23] defines a chemotherapeutic agent as one which deprives the inhibited organisms of the use of enzymes or metabolites by various types of interference. The organism thus becomes nutritionally more exacting than in its normal state and its new demands can, with due consideration for extraneous effects, be analyzed by the usual technics of bacterial nutrition.

The strongest samples of penicillin which can inhibit sulfonamide resistant gram-positive bacteria have been analyzed.[24] The formulas $C_{14}H_{19}NO_6$, $C_{24}H_{32}O_{10}N_2Ba$ and $C_{24}H_{34}O_{11}NSr$, represent results for the free acid with 240 units,[2] the barium salt with 450 to 500 units[25], and the strontium salt with up to 750 Oxford units per mg.[26] The single nitrogen in the last formula is believed to be incorrect, as it does not agree with proper indications.[23]

According to Gardner[27] the growth of organisms in the presence of penicillin temporarily continues unaccompanied by cell division and is followed by lysis. This was confirmed by other workers[28, 29, 30] but the mechanism is still unknown.

Penicillin apparently does not prevent oxygen uptake by susceptible organisms. The latter continue to elongate but do not divide, showing enlarged and involution forms.[27]

Mold cultures are grown in individual flasks on sugar solutions at 24° C. Penicillin formed on mold pass into the media and are decanted. These illustrations are presented through the courtesy of E. R. Squibb and Sons, Inc., one of three original firms working on penicillin. The others are Merck and Pfizer.

22. McIlwain, H.; *Biochem. J. 35*:1311 (1941).
23. *Ann. Rev. Biochem. XII*:562 (1943).
24. Powell, H. M.; and Jamieson, W. A.; *Proc. Soc. Exper. Biol. Med. 49*:387 (1942).
25. Abraham, E. P.; and Chain, E.; *Brit. J. Exper. Path. 23*:103 (1942).
26. Catch, J. R.; Cook, A. H.; and Heilbron, I. M.; *Nature 150*:633 (1942).

Penicillin B

Recently Roberts and his colleagues[14] report on three different strains of *Penicillium notatum*, originating in the strain isolated by Fleming. When these different strains are grown they produce another form of penicillin. This has been called "penicillin B" and is readily soluble in water. It is insoluble in lipid solvents. In the dry form, it is stable. It possesses a potency of approximately 50,000 Oxford units per milligram. This product is considered to be different to the "accepted" penicillin, the latter perhaps could be termed "penicillin A",— but is not so named.

Penicillin B is active against some gram-positive forms, including the *Staphylococcus aureus*, as well as against gram-negative bacteria. Its drawback lies in the fact that it is toxic to mice, when injected subcutaneously. In investigations it has been found that 2.5 mgm., or 30,000 to 50,000 Oxford units, when administered subcutaneously will cause death of mice in 3 to 24 hours. It is possible to tolerate larger quantities by giving small repeated doses. Penicillin B would be more desirable than the "A" if it would be freed of this toxic activity, as it is far more stable. However, it should be of some value in local use.

Esters of Penicillin

Meyer and his colleagues[2] recently reported the preparation of methyl and ethyl esters of the free acid of penicillin. They were prepared by reacting the free acid with the corresponding diazo compound. The esters thus formed are insoluble in neutral or slightly alkaline buffers, very soluble in benzene and are not precipitated from chloroform-benzene solutions by dry ammonia. *In vitro* tests showed that the aliphatic esters have an activity of approximately 25 micrograms per cc., in contrast to 0.08 to 0.3 micrograms per cc. for the original penicillin fractions, against hemolytic streptococci. This contrasting low activity is explained as being due to a partial hydrolysis of the esters by the hemolytic streptococci.

In mice a marked activity was shown by the esters. Mice, infected with pathogenic organisms, were given the drug subcutaneously two hours after infection and for from two to three days. The esters appeared to be highly protective for mice against lethal intraperitoneal doses of a highly virulent strain of hemolytic streptococci. The ethyl ester was superior in activity. The benzohydryl ester mixture, however, is hydrolyzed by the test organism and has no greater activity than the starting compound. Acetylation of penicillin makes it more alkali-stable.

Organism

The organism employed is *Penicillum*. Several species have been employed at various times to produce penicillin, namely *P. notatum* Westling, *P. chrysogenum* Thom, *P. cyano-fulvum* B., *P. rubrum*, and *P. baculatum* Westling, and a number of other strains which show satisfactory yields. Most laboratories have concentrated on the *P. notatum*. Variance of ability to produce penicillin is noted under changed conditions of culture.

Unitage

Robinson[15], as with other workers, has recently reported experiments which he conducted on "the toxicity and efficacy of penicillin" which was based upon Oxford (Florey) units. A "Florey unit" and an "Oxford unit" are identical, and is that amount of penicillin which when dissolved in 50 cc. of meat extract broth just inhibits completely the growth of the test strain of *Staphylococcus aureus*. The arbitrary unit for the British workers is the Oxford unit, which is (until penicillin is obtained chemically pure) that amount of penicillin which when dissolved in 1 cc. of water gives the same inhibition as this standard. The material used in the human therapeutic tests usually contained 40-50 of these units per mgm. but now not less than 100 Oxford units per mgm.

Method of Assay

The serial dilution method used by Fleming[3] which measures the lowest concentration of penicillin that will prevent growth of the test-organism in broth, is laborious and can only be applied to sterile material. This method resembles the usual N.I.H. staphylococcus determination using 24-hour cultures, standard loops, etc. This at once reduces its usefulness for chemical investigations, for the material to be

27. Gardner, A. D.; *Nature 146:*837 (1940).
28. Smith, L. D.; and Hay, T. J.; *J. Franklin Inst. 233:*598 (1942).
29. Discussion of Biochem. Soc.; *Biochem. J. 36:*1 (1942).
30. Oxford, A. E.; *Biochem. J. 36:*438 (1942).
31. Richards, A. M.; *J. A. M. A. 122:*235 (1943) #4.

tested would have to be sterilized by filtration and it seems that under some conditions penicillin may be partially absorbed on Seitz filter pads.

Selection of Method

The cup method is by consensus the more desirable method due to economy of time. The dilution method may include such as penatin, penicillin B and notatin in the assay. Penatin and notatin are protein materials not assayed by the cup method. Some workers use the N.I.H. serial dilution method and check it against the cup process. In the former the test hinges on the last tube showing no growth. The pH of the media is an influencing factor. Some laboratories employ *B. subtilis* in place of *S. aureus*. Other laboratories desire a mouse-protection test *in vivo*.

Accuracy

High accuracy cannot be claimed for the methods of assay, but if they are done in triplicate and if the unknown is diluted properly the error is probably not greater than $\pm 25\%$ and may be considerably less. There is no evidence that under suitable conditions the cup method is inferior in accuracy to the serial dilution method and it is many times quicker. In addition, less than 0.25 cc. of fluid is required for each test.

Factors influencing accuracy of the method are (1) depth of agar; (2) determination of exact edge of inhibition zone; (3) size of cylinders; (4) the pH of medium; (5) use of standard organism and (6) time and technic.

Assuming the identity of results by the agar plate method, comparisons can be made against serial dilution readings, however.

Production

In an introductory statement by Richards,[31] chairman of the Committee on Medical Research, the significant fact is expressed that penicillin is difficult to produce on a large scale. In the mold's normal metabolism only very minute amounts of penicillin are formed, and those only after several days' time. It is understood that more than 20 liters of culture fluid are required to yield one gram of the substance and even that yield is considered high by many. The solution must be pure in order to have a stable product. Normally, culture media are highly susceptible to attack by bacteria, a factor readily understood. Such an attack destroys the penicillin. It has been believed that when contamination occurs, the penicillin which had been produced is destroyed by the contaminant. Also, inoculation with *P. notatum* and a contaminant at the same time prevents penicillin production. In the work done on penicillin a great deal of effort has been consumed in seeking the most productive strains of the mold, the best culture fluids, methods for extraction, purification and stabilization.

An additional problem is the prevention of deterioration of penicillin. All of these factors at present affect the program which is being set up for large scale production of the drug.

Media

The mold will grow and produce penicillin on a variety of different media, but that used by Clutterbuck *et al*,[20] consisting of sodium nitrate, potassium acid phosphate, potassium chloride, magnesium sulfate, ferrous sulfate, glucose and water was generally adopted with peptone, yeast extract and other materials added. The medium sterilized by autoclaving, is sown with a spore suspension. Twenty-four hours after sowing a very delicate fluffy gauze-like growth can be seen with difficulty on the bottom of the vessel (at 24° C). The growth becomes more voluminous during the next day and on the 3rd day, throws up dry white mycelium. Usually by the 4th or 5th day the mycelium begins to turn bluish green. The growth consists of a continuous, compact, often corrugated, dark greenish-blue felt whose upper surface cannot be wetted by water. The under surface is wetted, and is brownish-yellow and slimy. As incubation is prolonged the color of the mycelium becomes more faded and grey.

The changes in the appearance of the mold are accompanied by changes in the pH of the medium, which starts between 6 and 7 and may fall as low as 3 by the 3rd day—usually as the dry mycelium is forming. It then rises, reaching 5 as the greenish-blue color appears. At this stage a faint yellow color can be seen in the medium and traces of penicillin can be detected. The pH continues to rise and the titre of penicillin and the yellow color both increase rapidly. As the mycelium becomes more faded the pH rises more and more slowly; it seldom exceeds 8.8. Penicillin production is usually at its maximum at about pH 7, and may stay almost

constant for some days or may fall again rapidly. The pH is perhaps the most useful gauge of the state of the growth, apart from an assay for antibacterial activity.

Factors Affecting Yield

Chain and others have stated that penicillin production seems to take place over a wide range of oxygen tension. The mold will grow anaerobically. The mold grows satisfactorily at 24° C. At lower temperature growth is delayed. Fleming stated that the mold would not grow at 37° C.

When the medium is fit to be harvested in the shallow method it can be drawn off from under the mycelium and replaced with fresh medium in which more penicillin will form in about half the time required for the initial production.

The mold must be grown and the medium harvested and replaced under strictly sterile conditions since penicillin is destroyed by certain bacteria, according to Abraham and Chain.

Occasionally a batch produces little or no penicillin. Although this can generally be traced to bacterial contamination in some instances contamination could not be proved, and there is suspicion that penicillin production may be a variable and easily disturbed function of the mold.

Variation in Media

The media preferred by some American workers for the production of penicillin consists of lactose as a carbon source rather than glucose or brown sugar (preferred by others), added to the basic medium described heretofore (Czapek medium), with added corn steep liquor. A number of other media are employed by some producers, such as corn meal, wheat bran, etc. The lactose fosters the culture by delaying alkalinization which is destructive to penicillin production, and prevents gluconic acid formation.

Penicillin is an exceedingly labile compound more sensitive to hydrogen ion concentration than any other factor. Since it is an excellent organism for conversion of glucose to gluconic acid, care must be taken to avoid high concentrations of glucose or other sugars so oxidizable. Carbonates are employed to control this change.

Production Technics

Two general methods of production are presented and are being employed experimentally. The *"shallow"* or *"surface"* method which employs glass or ceramic flat bottles or flasks, and the *"deep"* or *"submerged"* method, using large vats or tanks as in brewing. In both methods, penicillin is produced best at pH 7.0 to 8.5.

The shallow method allows the medium to be sterilized in the flasks, which are then laid flat and inoculated with a few drops of a suspension of the organism and incubated at 24° C. The penicillin-containing fluid is withdrawn for harvesting and re-inoculated. The deep method provides large 500 gallon to 6,000 gallon tanks of sterile media which are inoculated and cultured.

Extraction from Culture Medium

Penicillin can be extracted by ether, amyl acetate and certain other organic solvents from an aqueous solution whose pH has been adjusted to 2. From the organic solvent the penicillin may be re-extracted by shaking with phosphate-buffer or with water the pH of which is kept at 5 to 7. Penicillin is quickly destroyed at pH 2 at room temperature, so the first extraction must be carried out rapidly and at a low temperature. Once it has been extracted into solvent the penicillin is stable for some days. The crude penicillin, having been filtered and acidified, is brought in contact with amyl acetate, to which the penicillin is given up. The crude solution is acidified immediately so that the aqueous solution is at a pH at which penicillin is unstable for only a

Shown below is penicillium mold growing on nutrient, with penicillin droplets forming on the surface.

few seconds before it has been extracted. As the crude solution is passed through a cooling coil surrounded by circulating tap-water probably very little destruction of penicillin takes place. Phosphoric acid is used for the acidification. It will therefore act as its own buffer. The solvent containing the penicillin has 1/10 to 1/5 of the volume of the crude solution from which the penicillin has been extracted, and many impurities, notably those forming emulsions, have been eliminated.

Processing

The penicillin-solvent material is again cooled and centrifuged. The emulsion of water and amyl acetate breaks and the latter is removed. The water residue is re-treated with amyl acetate. Barium hydroxide, calcium and sodium carbonates and magnesium oxide are also employed in the process, and an ether extraction step follows. A variation in coloration of the ether extract is noted, from brown to light yellow, the latter containing the most penicillin. After further buffering and extraction, the penicillin is removed in pyrogen-free water, resulting in an orange red fluid. Absorption also employs various aluminas for continuous extraction. The solution is quite stable and may be kept in a refrigerator or stored after lyophilization, which produces a feathery yellow powder. The "acid", and sodium, calcium, and magnesium salts may be made.

Some producers extract into aqueous solution from chloroform, followed by filtration through a bacteriological filter, and lypophilization, while another manufacturer employs direct dry ice freezing and vacuum desiccation.

The usual product contains not more than two per cent of moisture and usually from one-half to one per cent. The present product as marketed never contains over 10 per cent pure penicillin.

In the dry state, penicillin will be stable for from three to six months if maintained at 4° to 5° to 10° C. At room temperature it will lose one-third to one-half of its potency. Liquid preparations are unstable. Perfectly clear solutions can be made from the concentrate in pyrogen-free distilled water or isotonic or normal saline solution.

The final step in some cases consists of lyophilizing the product directly from a measured solution in the final ampul, while other producers prefer to desiccate the product in bulk, and weigh out measured quantities in ampuls in a moisture-free sterile chamber. Ten per cent excess is customarily allowed.

Sterility

Penicillin is presumptively sterile, and usual tests fail to show any other state.

The product must be pyrogen-free and the U.S.P. XII test employing 2,000 units per Kgm. of rabbit is satisfactory for establishing proof of the pyrogen-free state. The pyrogens if present, possibly can be removed by Seitz filtration although this is disputable.

Potency

The final product when produced will contain not less than 100 Oxford units per mgm., and usually much higher, as concentration lessens the possibility of protein reaction.

Administration

Herrell and others for economy administer the material by intravenous route, but Rammelkamp and Keefer show that intermittent injection produces high levels, but ultimate loss in a few hours. Thirty thousand to 40,000 units are customarily administered in the first day of treatment, in two liters of saline or dextrose, rapidly at first (100 to 200 cc.) and then at 30 drops per minute. Rate of injection is immaterial if blood level is maintained. Considerable variation in dosage has been reported, with as little as 8,000 units and as much as 600,000 units being given daily without untoward effect. Usually, staphylococcal (acute and chronic) cases require 100,000 units daily, with streptococcal, pneumococcal, and meningococcal infections requiring progressively lesser amounts. Bovine actinomycosis requires but little quantities, over a long period.

No toxicity has been shown for penicillin, with the only reactions shown due to pyrogens or to a normal febrile reaction traceable to too-rapid injection. Excessively large doses, comparable to human dosage, have been given to rabbits without ill effects, and no ill effect has been noted in clinical use. Penicillin appears in the urine in large quantities in an unchanged state.

Penicillin will probably be packaged in ampuls containing in each approximately 100,000 Oxford units. Smaller ampul contents may be approved if later need arises, especially in pediatrics. The use of Oxford units will continue until a pure or synthetized product is produced, probably in a year or so, when the mgm. will be employed as the standard unit.

Conclusion

The product is striking in that it combines to an extraordinary degree two most desirable properties of a chemo-therapeutic agent, low toxicity to issue cells and powerful bacteriostatic action. Its effect is noteworthy on a wide variety of bacterial species.

Penicillin has a much greater bacteriostatic power against staphylocci and streptococci, than do the sulfonamides. Regardless of the extent or volume of the infection and organisms, the product is equally effective, and much more so than the sulfonamide drugs. Hydrolytic protein breakdown products, tissue autolysis products or pus, which inactivate sulfonamides and other agents, have no effect on penicillin. Thus, in more than 500 patients in the United States and an almost equal number abroad treated with penicillin, results have been achieved which lead to the belief that the new agent is far superior to the sulfonamide drugs in the treatment of *Staphylococcus aureus* infections with and without bacteremia, including such conditions as acute and chronic osteomyelitis, cellulitis, carbuncles of the lip and face, pneumonia and empyema, and infected wounds and burns. In infections due to the hemolytic streptococcus, pneumococcus and acute and chronic gonococcus, which infections have been resistant to the sulfonamides, penicillin was found to be effective. It was ineffective in the therapy of subacute bacterial endocarditis.

notes

PENICILLIN

ITS USEFULNESS, LIMITATIONS, DIFFUSION AND DETECTION, WITH ANALYSIS OF 150 CASES IN WHICH IT WAS EMPLOYED

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The introduction of penicillin for treatment of bacterial infections is one of the most important developments in chemotherapy. The relative lack of toxicity of penicillin for most tissues is one of its great advantages. This lack of toxicity was apparent to Fleming [1] and to Florey and his associates.[2] It was further evident from studies carried out in our laboratories, which began early in 1941,[3] that penicillin was a highly antibacterial substance and at the same time possessed very low toxicity for tissue as measured by means of tissue culture methods. Although penicillin is exceedingly effective in treatment of some infections, it is ineffective against many others. One of the essential requirements for successful treatment of bacterial infections with penicillin is to limit its use to infections due to those pathogens which are known to be susceptible. At present the susceptible and the insusceptible organisms are essentially those listed in table 1. As the work progresses, other organisms undoubtedly will be added to the list.

The successful use of penicillin is attended by other problems not commonly encountered in the use of therapeutic agents. Penicillin therapy should be confined to institutions as long as it is necessary to administer the material intravenously or intramuscularly. Penicillin cannot be administered by mouth, because it is destroyed by the gastric acids. Neither can it be administered intracolonically, since it is destroyed by certain organisms present in the fecal stream.

The large scale preparation of penicillin has been accompanied by many difficulties which have necessitated careful control of release of the material. Because penicillin is extremely labile, it must be protected during its preparation against heat, changes in the p_H of the surrounding mediums, oxidizing agents and certain micro-organisms which elaborate substances which result in loss of potency of penicillin.

METHODS OF ADMINISTRATION

Local Application.—The broth filtrates of cultures of Penicillium notatum which contain penicillin were applied locally by Fleming [1] as early as 1929. In 1940 the Oxford investigators [2] reported the successful preparation of a purified penicillin which proved suitable for experimental studies and for treatment of infections due to susceptible organisms. Both the sodium and the calcium salts have been used for local treatment, but the calcium salt is more satisfactory. For local treatment of wounds involving soft tissue and bone and for topical application to infected surfaces, saline solutions containing 250 Oxford units per cubic centimeter are suitable. Recently the British investigators [4] have used penicillin locally in two other forms: 1. If a dry substance is desired, weighed amounts of penicillin are ground with sulfanilamide in a mortar until a homogeneous powder results. On occasions the final mixture contains as much as 5,000 Oxford units of penicillin per gram. The report by Ungar [5] suggests that penicillin and sulfonamides may have a synergistic effect. 2. Another preparation which the British have applied locally is a cream containing lanette wax, which contains 100 to 250 units of penicillin per gram.

In treatment of severe and extensive inflammatory lesions, uniformly satisfactory results are more likely to be obtained by systemic penicillin therapy alone or this in combination with local therapy.

Intrathoracic Instillation.—In treatment of suppurative intrathoracic disease, such as empyema, it is desirable to supplement parenteral therapy with instillation of penicillin into the pleural space. In many instances empyema thus can be satisfactorily treated without resorting to surgical drainage. For this purpose, as a rule, 30,000 to 40,000 Oxford units in 30 to 40 cc of isotonic solution of sodium chloride can be instilled directly following thoracentesis. This procedure is carried out once every twenty-four to forty-eight hours.

Intra-Articular Instillation.—Recently our studies have indicated that fairly adequate antibacterial amounts of penicillin reach the joint fluid following intramuscular or intravenous administration of the material to patients suffering with acute or subacute suppurative disease of joints. The concentration of penicillin in the joint fluid is in some instances approximately half that in the blood. If it is desirable to supplement systemic therapy, however, instillation of penicillin into the joint is not accompanied by any serious effects. We have instilled as much as 20,000 Oxford units in 10 cc. of isotonic solution of sodium chloride directly into a septic joint after aspiration has been performed. Studies on the length of time that penicillin will remain in the joint following instillation are mentioned later.

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Read before the Section on Miscellaneous Topics, Sessions for the General Practitioner, at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

Part of the penicillin used in these studies has been furnished by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

1. Fleming, Alexander: On the Antibacterial Action of Cultures of Penicillium, with Special Reference to Their Use in Isolation of B. Influenzae, Brit. J. Exper. Path. **10**: 226-236 (June) 1929.

2. Chain, E.; Florey, H. W.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J., and Sanders, A. G.: Penicillin as a Chemotherapeutic Agent, Lancet **2**: 226-228 (Aug. 24) 1940.

3. Heilman, Dorothy H., and Herrell, W. E.: Comparative Antibacterial Activity of Penicillin and Gramicidin: Tissue Culture Studies, Proc. Staff Meet., Mayo Clin. **17**: 321-327 (May 27) 1942; Comparative Bacteriostatic Activity of Penicillin and Gramicidin, abstr. J. Bact. **43**: 12-13 (Jan.) 1942.

4. Florey, H. W., and Cairns, H.: Penicillin in War Wounds: A Report from the Mediterranean, Lancet **2**: 742-745 (Dec. 11) 1943.

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TABLE 1.—*Antibacterial Action of Penicillin*

Susceptible Organisms	Insusceptible Organisms
Diplococcus pneumoniae	Eberthella typhosa
Streptococcus pyogenes	Salmonella paratyphi
Streptococcus salivarius	Salmonella enteritidis
Microaerophilic streptococci	Shigella dysenteriae
Staphylococcus aureus	Proteus vulgaris
Staphylococcus albus (some strains)	Pseudomonas aeruginosa (Bacillus pyocyaneus)
Neisseria gonorrhoeae	Pseudomonas fluorescens
Neisseria intracellularis	Serratia marcescens (Bacillus prodigiosus)
Actinomyces bovis	Klebsiella pneumoniae
Bacillus anthracis	Haemophilus influenzae
Bacillus subtilis	Escherichia coli
Clostridium botulinum	Staphylococcus albus (some strains)
Clostridium tetani	Micrococcus albus (some strains)
Clostridium perfringens (welchii)	Monilia albicans
Corynebacterium diphtheriae	Monilia candida
Vibrio comma	Monilia krusei
Micrococci	Blastomyces
Streptobacillus moniliformis	Mycobacterium tuberculosis
Borrelia novyi (spirochete of relapsing fever)	Streptococcus faecalis
Treponema pallidum	Brucella melitensis
Leptospira icterohaemorrhagiae	Plasmodium vivax
Spirillum minus	Toxoplasma
Psittacosis virus	
Ornithosis virus	

Intrathecal Instillation.—It will be evident, when diffusion of penicillin into the various tissues is considered, that in treatment of meningitis or infections involving the cerebrospinal structures it is essential to supplement systemic therapy by daily instillations of 10,000 to 20,000 Oxford units of penicillin into the spinal canal. This amount of penicillin usually is dissolved in 10 cc. of isotonic solution of sodium chloride. Both the sodium and the calcium salts of penicillin have proved satisfactory for this method of administration.

Subcutaneous Administration.—Penicillin may be administered intermittently or continuously by subcutaneous infusion. However, absorption of subcutaneous fluids is erratic and variable. Moreover, concentrated solutions of penicillin may be irritating when given subcutaneously. It appears, therefore, that the intravenous or intramuscular method of administration is preferable.

Intramuscular Administration.—Intermittent intramuscular administration of penicillin is a simple and practical method. Every three hours, 10,000 or 20,000 Oxford units, in 2 to 4 cc. of isotonic solution of sodium chloride is injected. A standard 20 gage intramuscular needle 2½ inches long is suitable. Local irritation may occur occasionally, and at least eight injections in twenty-four hours are required. The concentration of penicillin in the blood rises rather sharply during the first hour following intramuscular administration and then falls to a very low value during the hour before the next injection is made (fig. 1). Such rather sharp rises and falls of the concentration in the blood of any antibacterial agent are not, as a rule, desirable in the treatment of bacterial infections, particularly severe, overwhelming sepsis.

Intravenous Administration.—Penicillin disappears from the blood even faster after a single intravenous injection than after a single intramuscular injection. Further, intermittent intravenous injection requires eight separate venipunctures per day. This method has been used, however, in some instances with satisfactory results.

The continuous intravenous drip method of administering penicillin, which is used at the Mayo Clinic, has been described elsewhere.[6] The dose of penicillin given in twenty-four hours by this method has varied considerably with different investigators. For treatment of some types of infection, many investigators believe that administration of 200,000 to 300,000 Oxford units per day is necessary. We have used, as a rule, no more than 80,000 units per day and, in many instances, 40,000 units. When increased supplies of penicillin are available, the problem of dosage may become of less significance. In our early work with penicillin, low doses were employed to spread a small supply of penicillin as far as possible. If subsequent experience indicates that the hazard of delayed recurrence is increased by using low dosage, obviously the amounts used must be increased. We consider, however, that 100,000 units per day is probably the maximal amount of penicillin necessary for treatment of the infections most commonly encountered. Delayed recurrence, in the presence of metastatic lesions, may occur at times regardless of the amount of penicillin used.

Local venous irritation at the site of injection may attend use of the continuous drip method. It seems especially likely to occur with certain batches of penicillin which probably contain impurities. Careful inspection of the intravenous apparatus, and changing the site of injection at the first sign of irritation, usually are sufficient to cope with this difficulty. Although we have administered penicillin for as long as eight days through the same vein and at the same site of injection, often it is necessary to change the apparatus every few days. In our experience, venous irritation does not occur in more than 5 to 10 per cent of cases.

The continuous intravenous drip method is used by us almost entirely except when suitable veins are not available. Under these circumstances the intermittent intramuscular method is used. It is our impression that approximately twice as much penicillin is required for satisfactory intramuscular treatment as is required when the intravenous drip method is employed.

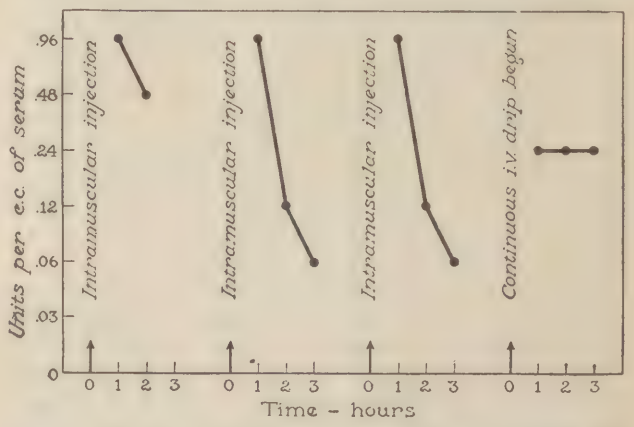

Fig. 1.—The falling serum concentration of penicillin in three hours when 50,000 units is administered by intramuscular injection and the approximately constant serum concentration when the same amount is given by continuous intravenous drip over the same period.

DIFFUSION OF PENICILLIN INTO VARIOUS TISSUES

Historical.—The test of the amount of active penicillin in the blood can be measured by the power of the blood serum to effect bacteriostasis. This is the test which lies behind use herein of the terms "penicillin

activity," "bacteriostatic activity," "concentration of penicillin" in the blood or in the tissue fluids, "blood level of penicillin," "penicillin content" and so on.

Florey and his associates [7] made the first report on distribution of penicillin in the body after it had been administered in different ways. From studies with experimental animals they found that penicillin disappeared rather rapidly from the blood after a single intravenous injection but that a large percentage of the amount administered was found in the urine. When penicillin was given by subcutaneous injection, the concentration in the blood was less but a detectable amount was present for a longer period than after a single intravenous injection. Penicillin, when administered by any route, was found in a more concentrated form in the bile than in the blood serum, but the total amount excreted by the liver was small compared with that excreted by the kidneys. Penicillin was absorbed from the intestine when care was taken to protect the penicillin from being acted on by the acid of the stomach. Regardless of the method of administration, penicillin was found in the saliva in lower concentrations than in blood collected at the same time. Tears, pancreatic juice and spinal fluid had no antibacterial activity when penicillin was given intravenously. When a single intravenous injection of penicillin was given to human patients there was an initial high level of penicillin activity in the blood, followed by rapid loss of activity; large amounts of pencillin were excreted in the urine. When penicillin was introduced into the small intestine by means of a duodenal tube, the substance was found in the blood for a longer period than after a single intravenous injection. Penicillin also was detected in the blood after it had been given by mouth along with adequate amounts of sodium bicarbonate.

The Floreys,[8] reporting further clinical experiences with penicillin, included data on the presence of penicillin in the blood. Rammelkamp and Keefer [9] and Rammelkamp and Helm [10] extended to human patients the observations made by Florey and his co-workers on experimental animals. In addition, Rammelkamp and Keefer found that when penicillin was injected into inflamed body cavities such as a knee joint, a suprapatellar bursa or an empyema cavity, or when it was introduced into the cerebrospinal fluid, it could be detected in the blood and it was found to be present for as long as twenty-four hours in the region into which it had been injected. There was some evidence that penicillin passed more rapidly from the cerebrospinal fluid into the blood when the meninges were inflamed than when they were not.

Fleming [11] reported quantitative determinations of the bacteriostatic power of blood and cerebrospinal fluid of a patient with streptococcic meningitis who had been treated with penicillin. In another study Fleming [12] described a technic to determine the blood levels of penicillin that result from intravenous and intramuscular injection of different amounts of penicillin. He showed that the presence of leukocytes along with specific antibodies for the test organism added to the bacteriostatic power of the blood when penicillin was present. Thus he was able to explain why a favorable clinical result may occur even though penicillin cannot be detected in the blood by any of the methods available at present. Fleming also found that when penicillin was injected into an axillary abscess its presence could be detected in the abscess twenty-four hours later.

Present Work.—Since it has been demonstrated by others that intermittent intravenous injections of penicillin are not satisfactory for maintaining an adequate level of penicillin in the blood, further investigations were not made along this line. We were interested particularly in determining the penicillin activity of the blood of patients who were receiving penicillin by the continuous intravenous drip method, which has been used, for the most part, in our clinical studies. Using Fleming's adaptation of the Wright slide cell technic, determinations were made on one specimen from each of 11 patients who were receiving 40,000 units a day by continuous intravenous drip. The serum of 6 of these patients gave a value of 0.12 unit per cubic centimeter; in the serum of 1 was 0.06 unit per cubic centimeter, the serum of 2 contained 0.03 unit per cubic centimeter and there was no penicillin in the serum of 2 patients. The blood of 1 of these last 2 patients gave no evidence of activity on three different occasions. When this patient was given 100,000 units of penicillin a day by continuous intravenous administration, the amount of penicillin present in the blood serum was 0.12 Oxford unit per cubic centimeter. In the blood of another patient who was receiving 80,000 units a day by intravenous drip also there was 0.12 unit per cubic centimeter.

A study was made of the penicillin activity of the blood following intramuscular injections. Three patients were given 50,000 units of penicillin by intramuscular injection every three hours, and the bacteriostatic activity of the blood was determined at hourly intervals. The results are presented in figure 1. Even with the comparatively large amounts of penicillin administered, the blood taken one hour after injection did not contain more than 1 unit per cubic centimeter. Significant amounts of penicillin were detected in the blood throughout the period of treatment.

The amount of penicillin in the urine varied greatly with a number of factors. Some of the conditions influencing the results were the amount of penicillin administered, the volume of urine excreted and the presence or absence of bacteria in the urine. The presence of coliform bacteria was accompanied by rapid loss of penicillin activity when the specimen was kept at room temperature. On several occasions urine which contained coliform bacteria and in which the concen-

6. Herrell, W. E.: The Clinical Use of Penicillin, an Antibacterial Agent of Biologic Origin, J. A. M. A. **124**: 622-627 (March 4) 1944.

7. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**: 177-188 (Aug. 16) 1941.

8. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**: 387-396 (March 27) 1943.

9. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425-437 (May) 1943. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342-350 (March) 1943.

10. Rammelkamp, C. H., and Helm, J. D.: Excretion of Penicillin in Bile, Proc. Soc. Exper. Biol. & Med. **54**: 31-34 (Oct.) 1943. Rammelkamp, C. H., and Helm, J. D.: Studies on the Absorption of Penicillin from the Stomach, ibid. **54**: 324-327 (Dec.) 1943.

11. Fleming, A.: Streptococcal Meningitis Treated with Penicillin: Measurement of Bacteriostatic Power of Blood and Cerebrospinal Fluid, Lancet **2**: 434-438 (Oct. 9) 1943.

12. Fleming, A., in discussion on Penicillin, Proc. Roy. Soc. Med. **37**: 101-104 (Jan.) 1944.

tration of penicillin was high soon after being voided (as much as 120 units per cubic centimeter) completely lost its penicillin activity after being kept in the icebox overnight.

What is now to be said relates to an earlier paragraph on intrathecal instillation. The observation of Rammelkamp and Keefer that penicillin does not pass from the blood into the spinal fluid in detectable amounts was confirmed. Four persons were given 100,000 units of penicillin a day by continuous intravenous administration. Two specimens of cerebrospinal fluid were taken from each patient while this treatment was in progress but none gave evidence of penicillin activity. When 10,000 units of penicillin was administered intraspinally, penicillin activity could be detected in the spinal fluid twenty-four hours later. Values varied from a trace of penicillin to 0.06 unit per cubic centimeter.

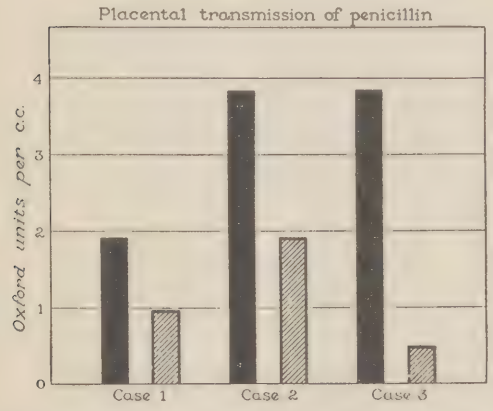

Fig. 2.—Columns represent penicillin found in blood: black columns, mother's blood; shaded columns, blood from umbilical cord. In the different cases 100,000 units of penicillin was administered at different intervals before delivery. In case 1 the interval was forty-five minutes, in case 2 fifteen minutes and in case 3 five minutes. In case 3 both mother's blood and blood from the umbilical cord gave positive complement fixation tests for syphilis.

Forty-eight hours after intraspinal administration of 10,000 to 20,000 units, no penicillin could be detected. Determinations were made three times on each of 3 patients.

In a consideration of the advisability of using penicillin in the treatment of antepartum syphilis it is of importance to know to what extent penicillin given to the mother will pass into the placental circulation and become available to the fetus. Consequently, three observations were made on human subjects. A large amount of penicillin (100,000 units) was given during a relatively short time to each of 3 patients toward the end of the second stage of labor. At delivery, a short time later, a sample of blood from the umbilical cord and a sample of blood from the anterior cubital vein of the mother were obtained simultaneously. In 1 instance blood from the mother and that from the umbilical cord both gave positive serologic tests for syphilis. The results of these tests are presented in figure 2. It is evident from these studies that penicillin is transmitted through the placenta and is available to the fetus whether the pregnant mother is without evidence of disease or whether she has syphilis.

SUITABLE METHODS FOR DETERMINING THE PRESENCE OF PENICILLIN IN BODY FLUIDS

We have studied various methods described by others of determining the presence of penicillin in body fluids.[13] Also we have attempted to develop methods that would be more sensitive and more reliable than those used at present.

A number of determinations of penicillin activity were made on various body fluids, using both Fleming's method and that of Rammelkamp on the same specimens. The same amount of penicillin standard usually caused inhibition of bacterial growth in both tests, but there was often a difference between the two tests of one dilution in either direction. Tests of penicillin activity of blood serum and other body fluids frequently gave different results by the two methods.

In order to determine which method was more reliable, known amounts of penicillin were added to human serum in the laboratory of Dr. Fordyce Heilman and the mixtures were tested as unknowns by both methods. In preparing the samples, normal human serum was divided into five portions. To one portion was added 1 cc. of 0.85 per cent sodium chloride solution for each 4 cc. of serum. A similar proportion of 0.85 per cent sodium chloride solution was added to each of the other portions but, previous to the addition, a different amount of penicillin had been mixed with each quantity of sodium chloride solution and the actual concentration in each instance was recorded. Small amounts of each mixture were put into glass tubes, numbered by code and stored in carbon dioxide. A few tubes were taken at random each day for a period of several days to be tested as unknowns by one of us (D. H.). The standard used in the tests was the same preparation used in making the unknown serum-penicillin mixtures. The results of these experiments are presented in table 2.

Fleming's method was found to be reliable for determining the actual penicillin content of serum.[13a] The percentage of variation between the results obtained with the slide cell technic and the actual penicillin content did not exceed the 50 per cent variation that is to be expected when serial dilutions are employed. The presence of a large proportion of serum did not decrease the sensitivity of the test in detecting small amounts of penicillin. Fairly small amounts of penicillin (0.06

13. Rammelkamp, C. H.: A Method for Determining the Concentrations of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**: 95-97 (Oct.) 1942. Fleming, A.: In Vitro Tests of Penicillin Potency, Lancet **1**: 732-733 (June 20) 1942. Dawson, M. H.; Hobby, Gladys L.; Meyer, K., and Chaffee, Eleanor: Penicillin as a Chemotherapeutic Agent, Ann. Int. Med. **19**: 707-717 (Nov.) 1943. Dawson, M. H., and Hobby, Gladys L.: The Clinical Use of Penicillin: Observations in One Hundred Cases, J. A. M. A. **124**: 611-622 (March 4) 1944. Gardner, A. D.: Morphological Effects of Penicillin on Bacteria, Nature, London **146**: 837-838 (Dec. 28) 1940. Fleming, A.: Personal communication to the authors. Abraham, Chain, Fletcher, Gardner, Heatley, Jennings and Florey.[7] Fleming.[11]

14. Herrell, W. E.; Heilman, Dorothy H., and Williams, H. L.: The Clinical Use of Penicillin, Proc. Staff Meet., Mayo Clin. **17**: 609-616 (Dec. 30) 1942.

15. Herrell, W. E., and Nichols, D. R.: The Calcium Salt of Penicillin, Proc. Staff Meet., Mayo Clin. **18**: 313-319 (Sept. 8) 1943.

16. Herrell, W. E.: The Role of Penicillin in the Treatment of Bacterial Infections, South. M. J. **37**: 150-156 (March) 1944. Herrell.[6] Herrell and Nichols.[15]

TABLE 2.—*Comparison of Fleming and Rammelkamp Methods Determining Penicillin Content of Serum*

Sample Number	Units per Cc. of Serum *	Fleming Method, Units per Cc.	Rammelkamp Method, Error, per Cent	Rammelkamp Method, Units per Cc.	Rammelkamp Method, Error, per Cent
1	4.00	3.84	4.0	3.84	4.0
2	0.06	0.06	0	0	...
3	0.06	0.06	0	0	...
4	4.00	3.84	4.0	3.84	4.0
5	1.30	0.96	26.2	0.96	26.2
6	1.30	0.96	26.2	0.96	26.2
7	0.06	0.06	0	0	....
8	1.30	0.96	26.2	0.96	26.2
9	1.30	0.96	26.2	0.96	26.2
10	0.25	0.24	4.0	0.12	52.0
11	0.25	0.24	4.0	0.12	52.0
12	0.06	0.06	0	0	....
13	0.06	0.06	0	0	....
14	4.00	3.84	4.0	7.68	92.0
15	4.00	3.84	4.0	7.68	92.0
16	0.25	0.24	4.0	0.24	4.0
17	0.25	0.24	4.0	0.24	4.0
18	0	0	0	0	0
19	0	0	0	0	0
20	0	0	0	0	0
21	0.25	0.24	4.0	0.24	4.0
22	1.30	1.92	47.7	1.92	47.7
23	4.00	3.84	4.0	7.68	92.0

* Samples were run as unknowns.

unit per cubic centimeter) were not detected by Rammelkamp's method and the results obtained were less uniform than those obtained with Fleming's test. In determining the penicillin content of the blood it is frequently desirable to be able to detect rather small amounts if they are present. It would seem that the Fleming test is superior in this respect to other quantitative methods available at present.

13a. The details of the method will be published elsewhere.

Fleming's method has certain other advantages. It is not necessary to use sterile technic in performing the test and material to be tested does not have to be filtered to insure sterility if it is tested soon after it is received. When the slide cell method is performed with micropipets very small amounts of the fluid to be tested are necessary and but little equipment is needed. The end point is easily determined, and the entire test is complete in eighteen hours. In the Rammelkamp test it is recommended that some of the contents of a few tubes near the end point be cultured on blood agar to insure sterility. This requires an additional twenty-four hour period in order to complete the test.

ANALYSIS OF RESULTS IN 150 CASES

Including the first case reported from the Mayo Clinic in which penicillin was used,[14] we have employed penicillin in the treatment of 150 patients suffering from infections owing to a variety of pathogenic bacteria. The present report deals with the results in these cases. The sodium salt of penicillin was used in 103 of the 150 cases. Two of us (W. E. H. and D. R. N.[15]) have reported previously on the calcium salt of penicillin. We have found it entirely satisfactory for local, intravenous, intramuscular and intrathecal use. It can be kept at room temperature for long periods without evidence of loss of activity. In studies[16] of cytotoxicity carried out in our laboratories, several preparations of the calcium salt proved less toxic than samples of the sodium salt tested in a similar fashion. The calcium salt was used in 47 of the cases herein reported.

Bacteremia.—At the time of preparation of the present report we had used penicillin in 28 cases of bacteremia. One of these cases will be counted again among the cases of meningitis. The organism identified in 25 of these cases was Staphylococcus aureus. An anaerobic streptococcus was isolated in 1 case, hemolytic streptococci in 1 and Neisseria intracellularis in 1. The sodium salt of penicillin was used in 16 of the cases and the calcium salt in 12. Twenty-five of the 28 patients recovered satisfactorily (89 per cent). The 3 patients who failed to recover all died of acute vegetative endocarditis and all had presented suggestive evidence of endocarditis at the time penicillin therapy was started. With 1 or 2 exceptions, all of these 28 patients were given the daily dose of penicillin previously recommended by us. In only 1 instance was there evidence of a delayed metastatic lesion which might possibly have been associated with the use of inadequate amounts. This case will now be reported:

A woman aged 20 was admitted at the clinic five days after onset of her illness, which had followed self-inflicted trauma to a furuncle on the chin. Subsequent to this trauma, extensive cellulitis had involved the chin, face and neck. Her temperature suddenly had risen to 105 F. Blood taken by her local physician had revealed Staphylococcus aureus on culture. She had been treated intensively with sulfadiazine. In spite of this the cellulitis had progressed rapidly and blood cultures had remained positive.

At the time of the patient's admission, the blood culture

Fig. 3.—*a*, appearance of patient at onset of penicillin therapy. Extensive cellulitis of mouth and face with extension into the cervical tissues. Staphylococcic septicemia. Patient gravely ill. *b*, appearance of patient seventy-two hours after treatment with penicillin was started. *c*, appearance of patient six days after penicillin therapy was started. Edema and cellulitis have practically disappeared. Complete recovery.

revealed 10 colonies of Staphylococcus aureus per cubic centimeter. The woman was unable to open the mouth or to swallow. She received 60,000 units of the calcium salt of penicillin daily by the intravenous drip method for nine days (total 540,000 units). A blood culture obtained twenty-four hours after use of penicillin had been started revealed 1 colony of Staphylococcus aureus per cubic centimeter. Blood cultures taken forty-eight hour after administration of penicillin had been started were negative, and three subsequent cultures were also negative. The temperature reached normal on the sixth day and remained normal thereafter. There was regression of the edema of the soft parts, and ninety-six hours after treatment had been started the patient could open the mouth without difficulty and was able to take a normal diet (fig. 3 *a*, *b* and *c*). On the twelfth day after admission, the patient was dismissed from the hospital and returned to her home. She felt well and made no complaints.

Several days after the woman had returned home, according to her account, she contracted a chest cold and a productive cough developed. She had a slight chill and a temperature of 103 F. and she also complained of pain in the left side of the thorax. She was treated with sulfamerazine by her local physician but, because of the persistence of her cough, she was readmitted at the clinic eighteen days after her dismissal. Blood cultures on readmission were negative. The bacteremia had not recurred nor was there any recurrence or difficulty with the initial lesion of the face. Roentgenograms of the thorax revealed a very small abscess in the upper lobe of the left lung. On this second admission the temperature was never higher than 98.6 F. Nevertheless, a second course of the calcium salt of penicillin was administered by the intravenous drip method. The patient received 80,000 units per day for seven days (total 560,000 units) and recovered.

The possibility of development of a delayed questionable metastatic lesion may argue in favor of higher doses. On the other hand, it would be interesting to know the incidence of delayed recurrence in the presence of systemic infections of this type when even larger doses had been administered as a routine.

Subacute Bacterial Endocarditis.—Early in the course of our studies, penicillin was used in 4 cases of subacute bacterial endocarditis. In 2 of these cases a nonhemolytic streptococcus was the organism isolated, and in the other 2 cases a micrococcus was isolated. In all 4 cases treatment resulted in failure. The blood cultures in 1 of these cases became negative and remained negative for several months, but the patient died of heart failure. It seems apparent that the usual doses of penicillin are ineffective against subacute bacterial endocarditis. Recent reports from elsewhere, however, indicate that in early cases encouraging results have been obtained when 200,000 units or more of penicillin is given daily.

Final evaluation of results in the treatment of subacute bacterial endocarditis will depend on further observations.

Severe Cellulitis Without Bacteremia.—Penicillin was used in 25 cases of severe cellulitis without bacteremia. Streptococcus pyogenes was the organism isolated in 13 cases. In 9 Staphylococcus aureus was the organism of infection. In 3 the infections were with mixed organisms, including anaerobic streptococci, green producing streptococci and Vincent's spirillum. The results were satisfactory in 22 of the 25 cases. Failures or doubtful results were obtained in 3.

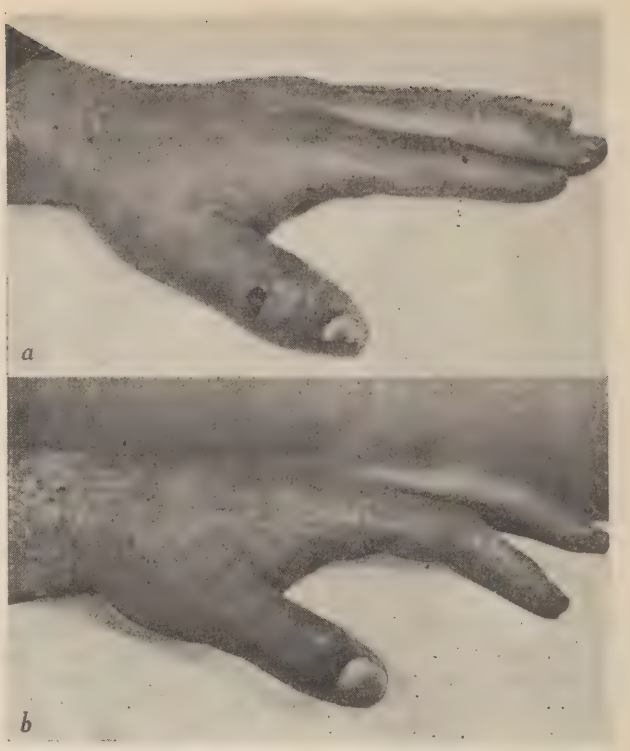

Fig. 4.—*a*, draining sinus of thumb associated with osteomyelitis of the interphalangeal joint; cultures positive for Neisseria gonorrhoeae. *b*, appearance of thumb after penicillin therapy. Sinus completely healed. No limitation of motion in joint.

Postoperative Wound Infection.—Penicillin has been used in the treatment of 8 very severe postoperative wound infections. In most instances the organism isolated from these wounds was Streptococcus pyogenes or Staphylococcus aureus. In 5 of these cases both organisms were present. The results were entirely satisfactory in 7 of the 8 cases.

Osteomyelitis.—Penicillin has been used alone or in combination with surgical measures in 22 cases of osteomyelitis. Since penicillin is active against most strains of Staphylococcus aureus as well as against the microaerophilic streptococci, it was reasonable to hope early in the course of studies on penicillin that it would prove effective in the treatment of osteomyelitis. Of the 22 cases of osteomyelitis, 11 were of the acute or subacute type. Of the 11, 9 were examples of spreading osteomyelitis of the maxillary or frontal bone, in which the organism isolated was the microaerophilic streptococcus. Penicillin, combined with surgical eradication of the diseased bone, yielded a satisfactory recovery in all 9 cases. There were 2 cases of acute fulminating osteomyelitis involving the long bones due to Staphylococcus aureus. Both patients recovered, although it was necessary to resort to surgical drainage in both cases. It may be possible that osteomyelitis of the flat bones responds more satisfactorily than osteomyelitis of the long bones.

In 11 cases of chronic osteomyelitis, penicillin has been used in treatment. The results are listed tentatively as doubtful in 10 and satisfactory in 1. Long observation must precede definite conclusions. In any

event, it must be stated again that thorough surgical drainage and eradication of foci play important parts in the successful treatment of this disease.

Gas Gangrene.—Penicillin has been employed in treatment of 6 patients suffering with gas gangrene. Organisms predominantly present in these cases were Clostridium welchii and anaerobic streptococci. In 1 of the cases antitoxin was not used. In the remaining 5 cases antitoxin and, in some instances, surgical treatment were combined with penicillin. The results were satisfactory in 4, and failures occurred in 2 instances. We feel, as do the British investigators,[17] that antitoxin must be combined with penicillin. While penicillin may definitely inhibit the growth of the organisms associated with gas gangrene, the neutralizing effect of antitoxin is essential.

Sulfonamide Resistant Gonorrhea.—Since the first report [18] on experimental and clinical effectiveness of penicillin in sulfonamide resistant gonorrhea penicillin has been found an exceedingly effective agent in treatment of this disease. Although we have treated a total of only 19 patients, all 19 have had satisfactory results. Two of these patients were suffering with gonorrheal arthritis in addition to sulfonamide resistant urethritis. The symptomatic response of the arthritis was striking. The arthritis was cured in both cases without instillation of penicillin into the joint. In 1 instance the arthritis involved the knee and in the other case the interphalangeal joint of the thumb. In this instance a draining sinus was present and cultures from this sinus revealed Neisseria gonorrhoeae. Roentgenograms revealed suppurative arthritis, with osteomyelitis. Without surgical intervention, complete healing resulted and roentgenograms after treatment were negative. This lesion, before and after treatment, is represented in figure 4 *a* and *b*. It is rarely necessary to use more than 100,000 to 150,000 units of penicillin as a total dose in the treatment of uncomplicated genitourinary neisserian infections. It may be necessary to use more in certain cases in which the condition is complicated by arthritis, endocarditis and so forth.

Actinomycosis.—Twelve patients with maxillofacial, thoracic or abdominal actinomycosis have been treated with penicillin. In 2 cases the treatment is listed as having failed and in 2 as having given satisfactory results. The remaining 8 of the 12 patients have not been followed long enough to justify final statements as to the outcome, and for that reason results in these 8 cases are listed as doubtful. Before a final report on actinomycosis is submitted, it is planned to follow these patients for at least eighteen months. At that time a detailed report on sensitivity of the organism, methods of treatment and results will be made.

Infections of the Urinary Tract.—Infections of the urinary tract due to susceptible organisms, such as Staphylococcus aureus, respond satisfactorily to penicillin. Seven patients have been treated. In 4 cases the result can be considered entirely satisfactory. In 3 the result was doubtful or failure resulted because of the ineffectiveness of penicillin against gram-negative organisms such as Proteus, Pyocyaneus and Escherichia coli.

Meningitis.—Penicillin was used in treatment of 4 patients suffering with meningitis. Two of these cases were examples of meningitis due to Neisseria intracellularis, in 1 of which there was an accompanying bacteremia and in 1 of which there was not. The patient suffering with meningitis and bacteremia recovered; the other died. The infection of both patients had resisted sulfonamide therapy. Of the 2 other cases in which penicillin was used, 1 was an example of meningitis due to an anaerobic streptococcus. In this case the spinal fluid became negative under penicillin therapy and it appeared that the meningitis had responded satisfactorily. On the other hand, the patient died of an abscess of a frontal lobe of the brain. The fourth patient suffered with overwhelming meningitis due to staphylococci; the patient died. All these patients received, in addition to intravenous or intramuscular therapy, daily intrathecal injections of penicillin in the amounts outlined in the paragraph on intrathecal instillation.

Pulmonary Suppurative Disease.—Penicillin was used in the treatment of 6 patients suffering with pulmonary suppurative disease. Included in this group were pneumonia, pulmonary abscess and empyema. The results were satisfactory in 5 of the 6 cases. Failure occurred in the treatment of a man aged 66 who was suffering from extensive bilateral postoperative pneumonia due to Diplococcus pneumoniae, type III. In spite of intensive penicillin therapy, the patient died.

Miscellaneous Diseases.—Listed under miscellaneous diseases are 10 cases, in 6 of which satisfactory results were obtained. Of the 6 patients who obtained satisfactory results 4 had suppurative disease of the middle ear or mastoid process. Infection in all 4 had resisted sulfonamide therapy and all recovered. The organism isolated in 3 of the 4 cases was Staphylococcus aureus and, in 1, Streptococcus pyogenes was the infecting organism. Of the other 2 of the 6 cases in which the results were satisfactory 1 was an example of extensive ophthalmitis and conjunctivitis due to Neisseria intracellularis. In the other the organism isolated from the throat was Corynebacterium diphtheriae.

The 4 cases in the miscellaneous group in which failure occurred included 1 case of bilateral otitis media in which the infection was complicated by severe enteritis; the patient was an infant and the causative organism was the Staphylococcus aureus. One case represented

17. Discussion on Penicillin, Lancet **2**: 638-639 (Nov. 20) 1943.
18. Herrell, W. E.; Cook, E. N., and Thompson, Luther: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289-292 (May 29) 1943.

19. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**: 355-356 (Dec.) 1943; Am. J. Pub. Health **33**: 1387 (Dec.) 1943.
20. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Relapsing Fever, Proc. Staff Meet., Mayo Clin. **18**: 457-467 (Dec. 1) 1943; Penicillin in the Treatment of Experimental Leptospirosis Icterohemorrhagica (Weil's Disease), ibid. **19**: 89-99 (Feb. 23) 1944.
21. Lourie, E. M., and Collier, H. O. J.: The Therapeutic Action of Penicillin on Spirochaeta Recurrentis and Spirillum Minus in Mice, Ann. Trop. Med. **37**: 200-205 (Dec. 31) 1943.
22. Augustine, D. L.; Weinman, D., and McAllister, Joan: Rapid and Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in the Treatment of Trypanosomiasis (Trypanosoma Lewisi) and Toxoplasmosis, Science **99**: 19-20 (Jan. 7) 1944.
23. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Infections with Spirillum Minus and Streptobacillus Moniliformis (Rat Bite Fever), Proc. Staff Meet., Mayo Clin. **19**: 257-264 (May 17) 1944.

severe brucellosis with brucella bacterial endocarditis. In 1 case acute leukemia was accompanied by secondary infection of the jaw, and the fourth failure occurred in a case in which penicillin was tried against induced malaria due to Plasmodium vivax. The results in the entire series are listed in table 3.

Comment on the Analysis of Cases.—It is evident from examination of the clinical results just reported that penicillin is an effective agent in treatment of practically all of the staphylococcic infections, whether or not bacteremia is present, with the possible exception of chronic osteomyelitis. These infections include extensive cellulitis, meningitis, pulmonary suppurative disease, suppurative disease of the kidney and infected wounds. Penicillin is equally effective against hemolytic streptococcus infections with or without bacteremia. It appears to be effective in the treatment of gas gangrene and anaerobic streptococcus infections. It is effective against sulfonamide resistant infections with Diplococcus pneumoniae and against all of the sulfonamide resistant gonorrheal infections, including complications commonly encountered in this disease.

TABLE 3.—*Results of Treatment with Penicillin in 150 Cases*

Clinical Diagnosis	Cases	Results		
		Satisfactory	Doubtful	Failure
Bacteremia	28	25	..	3
Subacute bacterial endocarditis	4	..	..	4
Severe cellulitis without bacteremia	25	22	1	2
Postoperative wound infection	8	7	..	1
Osteomyelitis				
Acute	11	11	..	..
Chronic	11	1	10	..
Gas gangrene	6	4	..	2
Sulfonamide resistant gonorrhea	19	19	..	..
Actinomycosis	12	2	8	2
Infection of urinary tract	7	4	1	2
Meningitis	4	1	..	3
Pulmonary suppurative disease	6	5	..	1
Miscellaneous diseases	10	6	..	4
Total	151*	107	20	24

* 151 diagnoses because of 1 patient who had both bacteremia and meningitis.

Further observation will be necessary; however, penicillin appears to be promising in the treatment of certain types of infections due to Actinomyces bovis. One of the most interesting observations in connection with studies on penicillin is that which concerns its antispirochetal action, first reported by Mahoney, Arnold and Harris.[19] Since the report by Mahoney and his associates,[19] F. R. Heilman and one of us [20] have found penicillin to be effective against other spirochetal infections, including relapsing fever and Weil's disease. Our experimental studies on relapsing fever have received confirmation in the reports by Lourie and Collier [21] and by Augustine, Weinman and McAllister.[22] It would appear from the studies of Lourie and Collier and from the studies reported by Heilman and one of us [23] that penicillin is also effective against Spirillum minus, one of the etiologic organisms of rat bite fever. Clinical studies have not as yet been reported on the spirochetal diseases which we have studied in experimental animals. Evidence is accumulating that penicillin has a definite place in syphilotherapy.

CONTRAINDICATIONS TO PENICILLIN THERAPY

On the basis of present knowledge, use of penicillin should not be attempted in treatment of gram-negative bacillary infections such as undulant fever, tularemia or influenza, or in the treatment of infections due to the colon-typhoid-dysentery group of organisms or to Friedländers' bacillus. Infections of the urinary tract due to the gram-negative organisms mentioned do not respond to penicillin therapy. At present it appears that penicillin should not be employed in the treatment of tuberculosis, acute rheumatic fever, lupus erythematosus, pemphigus, mononucleosis, leukemia, ulcerative colitis, malaria, blastomycosis and certain virus infections. On the other hand, the experimental work of F. R. Heilman and one of us [24] strongly suggests that penicillin may prove of value in the treatment of at least two virus infections in man; namely, ornithosis and psittacosis.

REACTIONS

Clinical experience with penicillin indicates that its use is not attended by many serious toxic reactions. There has been no evidence of disturbance in the peripheral blood or in the hemopoietic system. On the contrary, penicillin can be successfully used in the presence of pronounced anemia or pronounced leukopenia or even complete agranulocytosis. We have repeatedly seen suppressed leukocyte counts rise during the course of penicillin therapy in the face of overwhelming infection associated with suppression of the bone marrow. No evidence of renal toxicity has been seen.

The local irritation at the site of intramuscular and intravenous injection of penicillin already has been dealt with.

As long as pyrogen free penicillin is used, febrile reactions are not likely to occur. Cutaneous sensitivity to penicillin itself, or perhaps to impurities in the preparations, has been observed in only 2 of 150 cases. In both instances the reaction occurred when penicillin from one commercial source was being administered. When urticaria or dermatitis develops as the result of sensitivity to penicillin, great caution must be used in continuing to administer the material. Persistence of treatment in the face of a generalized cutaneous reaction might lead to development of exfoliative dermatitis. The skin of many persons is known to be sensitive to various molds and mold products. This cutaneous toxic reaction may become of more significance as penicillin is more generally used.

SUMMARY AND CONCLUSIONS

Penicillin therapy should be confined to infections due to pathogens known to be susceptible to its action.

Serious toxic reactions have not followed use of either the sodium or the calcium salt for intrathoracic, intra-articular or intrathecal instillation; nor have such reactions attended local application or intramuscular or intravenous administration in the doses recommended.

Local irritation at the site of injection of either the sodium or the calcium salt of penicillin varies with different batches. Changing the site of administration or changing the product often will terminate this reaction. The only other toxic reaction of any significance is the occurrence of urticaria and irritative dermatitis. The latter reaction is very infrequently seen. Febrile

24. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Ornithosis, Proc. Staff Meet., Mayo Clin. **19**: 57-65 (Feb. 9) 1944; Penicillin in the Treatment of Experimental Psittacosis, ibid. **19**: 204-207 (April 19) 1944.

reactions may occur if the penicillin employed is not pyrogen free.

The continuous intravenous drip method of administration of penicillin best maintains a constant level in the blood.

While penicillin diffuses fairly readily into most tissues, it does not reach the spinal fluid following intravenous or intramuscular injection. It is necessary, therefore, to administer penicillin by the intrathecal route at least once daily in treatment of infections involving the cerebrospinal structures. Following intravenous administration of penicillin, antibacterial amounts of the material reach the fluid of septic joints. Likewise, penicillin is transmitted through the placenta from the mother to the fetus. This is important in penicillin therapy for antepartum syphilis.

We believe Fleming's adaptation of the Wright slide cell technic to be the most reliable method of determining the penicillin content of serum.

Of 150 patients suffering with infections owing to a variety of pathogenic bacteria, 103 were treated with the sodium salt of penicillin and 47 with the calcium salt. The calcium salt is handled more easily and appears more stable. Among 28 patients suffering with bacteremia, most of whom had resisted sulfonamide therapy, 25 recovered and 3 died. At present, 80,000 units in twenty-four hours appears to be the most satisfactory dose in cases of bacteremia.

Other bacterial infections for which we have used penicillin include bacterial endocarditis, severe cellulitis, postoperative wound infection, osteomyelitis (acute and chronic), gas gangrene, sulfonamide resistant gonorrhea, actinomycosis, infections of the urinary tract, meningitis, pulmonary suppurative disease and a small group of miscellaneous infections. The results with 107 patients (1 of whom was counted twice, as is explained in table 3) could be considered brilliant or satisfactory; doubtful results or failures occurred with 44.

The use of penicillin should not be attempted in the treatment of gram-negative bacillary infections, including undulant fever, tularemia, influenza, infections due to the colon-typhoid-dysentery group or infections due to Klebsiella pneumoniae. Infections of the urinary tract due to gram-negative organisms do not respond to penicillin. It has not proved useful in treatment of tuberculosis, acute rheumatic fever, lupus erythematosus, pemphigus, mononucleosis, leukemia, ulcerative colitis, malaria or blastomycosis.

ABSTRACT OF DISCUSSION

Dr. Walter S. Priest, Chicago: I concur that the constant intravenous drip is the method of choice whenever feasible. It is possible to give the intravenous drip as slowly as 8 to 12 drops per minute continuously over periods of days without removing the needle, and that enables one to keep down the fluid intake where that is necessary. I have not been as fortunate as Dr. Herrell in regard to venous irritation, but I find, as he does, that it is not significant and that permanent thrombophlebitis has been a rarity. The reaction subsides promptly. Regarding the intramuscular administration, I have had one experience in which the patient had less irritation by using a more concentrated solution, up to 15 or 16 thousand units per cubic centimeter instead of the more usual 5 thousand. Dr. Herrell's comments on the use of 80 thousand units for twenty-four hours are noteworthy. Perhaps I have fallen into the habit of using larger doses unnecessarily. Since the present ampules are put up with a hundred thousand units per cubic centimeter it may be more practical to start with that as the initial twenty-four hour dose, by whatever method given, giving a somewhat larger dose at first and then adjusting the dose up or down as the patient's reaction seems to warrant. Certainly the smallest dose necessary to get the result is the one which should be used. During the past year I have had an opportunity to study the use of penicillin in large doses in 8 cases of subacute bacterial endocarditis. The infective organisms were of the viridans group, the hemolytic streptococcus group and the nonhemolytic nonrenal recrudescent streptococci. These patients received from 100 thousand to 400 thousand units of penicillin in twenty-four hours by the continuous intravenous drip method over a period of not less than four weeks. Out of this group, 2 are apparently cured, 1 is fever and bacteria free but still with an elevated sedimentation rate, 2 appear to be frank failures but are still alive, and 3 have died during the course of treatment. Has Dr. Herrell had any experience in the treatment of bronchiectasis with pencillin?

Dr. K. R. Brown, Des Moines, Iowa: I want to know whether Dr. Herrell finds penicillin effective in cavernous sinus thrombosis complications from facial cellulitis.

Dr. Wingate M. Johnson, Winston-Salem, N. C.: Dr. Herrell gave an exhaustive list of diseases in which penicillin is indicated and in which it is not. I don't believe he mentioned one important group, the rickettsial diseases.

Dr. Wallace E. Herrell, Rochester, Minn.: The point which Dr. Priest raised as to whether or not higher concentrations might have prevented the three failures in the cases of bacteremia deserves consideration. We find that administration of 80 thousand units in twenty-four hours results in a concentration of penicillin which is adequate to inhibit the organisms. Since most of the penicillin is dispensed in ampules of 100 thousand units I am inclined to agree that in general practice it would probably be worth while to use the contents of the 100 thousand unit ampule in preparing the twenty-four hour dose. Excluding bacterial endocarditis, however, we still do not feel that 200 to 300 thousand units per day is necessary to obtain satisfactory results in cases of bacteremia when the agent is administered by the intravenous drip method. The penicillin content of the blood of a patient receiving around 80 thousand units per day will usually be found to be somewhere around 0.06 to 0.12 Oxford unit per cubic centimeter, which is adequate to cause complete inhibition and keep the blood sterilized. In the 3 individuals who failed to recover, necropsy revealed acute ulcerative endocarditis. All 3 had heart murmurs and other clinical signs suggestive of endocarditis at the time penicillin therapy was started. When endocarditis is present at the time one begins penicillin therapy, the results usually will not be satisfactory even when very large amounts of penicillin are administered; at least this has been our experience. Better results will be obtained in the treatment of patients with bacteremia when it is no longer necessary to defer penicillin therapy until sulfonamides have been tried and have failed. I am sure Dr. Priest feels that it is too early to evaluate these results completely, but it is well worth while to continue to treat these patients so long as the organism present in their blood is found to be sensitive to penicillin. Many of the organisms present in subacute bacterial endocarditis are not sensitive. Dr. Priest's remarks concerning the febrile reactions incident to intravenous therapy are extremely important. Old tubing and apparatus not carefully prepared will result in febrile reactions which are not truly due to the penicillin. One must use the same precautions that he would in any intravenous medication. The same precautions must also be rigidly observed when penicillin is given intramuscularly, to avoid the introduction of bacteria or foreign substances which might lead to the development of localized abscesses. It is well known that patients receiving penicillin intramuscularly eight times a day are liable to get "needle shy." We have not had any experience in the treatment of bronchiectasis per se, although we have used penicillin therapy with

encouraging results in preparation for lobectomy and in postoperative treatment. Concerning sinus thrombosis, it is safe to say that penicillin has resulted in a cure in many cases. I feel certain that 1 of our patients suffering from staphylococcic bacteremia had a sinus thrombosis and that he recovered as a result of penicillin therapy. This particular patient never regained vision in one eye. Concerning the effectiveness of penicillin against rickettsial infections, I might call attention to the experimental work reported by Pinkerton and his associates of St. Louis, which indicates that penicillin may prove effective against experimental typhus. Enough data have not yet been accumulated to warrant any statements concerning the clinical use of penicillin in virus infections. A virus may be quite susceptible to the action of penicillin and one may still not obtain a satisfactory clinical result, especially if the virus has become well fixed in the cells by the time one gets an opportunity to treat the patient.

5

THE CLINICAL USE OF PENICILLIN

OBSERVATIONS IN ONE HUNDRED CASES

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Following the announcement of the experimental results of the Oxford workers,[1] studies on penicillin were initiated at the Presbyterian Hospital in the autumn of 1940 and have been carried forward continuously up to the present time. The results of the biologic and chemical phases of the investigation have been reported from time to time elsewhere.[2] In the early stages of the work little attention was paid to the clinical aspects of the problem because of difficulties encountered in producing quantities sufficient for therapeutic purposes and because of the desire to utilize such material as became available for chemical and experimental studies. Enough material was produced, however, to demonstrate that the product was essentially nontoxic for man, and a limited number of patients were treated both locally and systemically.

For preliminary clinical trial, cases of subacute bacterial endocarditis were selected because of the known refractoriness of this disease to other methods of treatment and because many strains of Streptococcus viridans were shown to be susceptible to penicillin "in vitro." It soon became apparent that penicillin, as prepared in our own laboratories, was harmless except for occasional instances of pyrexia and that temporary improvement in the patient's condition with reduction in the number of colonies in the circulating blood could be effected. In no case, however, were the beneficial effects observed other than temporary, and treatment of cases of this disease was therefore abandoned until such time as larger supplies might become available. In the light of subsequent work it became obvious that the amount of penicillin given in this early group of cases was totally insufficient to secure a significant result.

During this stage of the investigation 3 cases of acute pneumococcic endocarditis came under observation. Since it was known that pneumococci were much more sensitive to penicillin than strains of Streptococcus viridans and since all 3 cases proved completely refractory to sulfonamide therapy, they were treated as intensively as possible. In 2 instances there was a dramatic temporary improvement with sterilization of the blood stream for a period, but both patients ultimately succumbed to their infection.

The first of these 2 cases was treated in March 1942. A man aged 53 was apparently recovering uneventfully from a lobar pneumonia (type 7) when he developed a septic temperature. Sulfonamide therapy in adequate dosage failed to improve the situation and a blood culture revealed 650 colonies of pneumococcus (type 7) per cubic centimeter. The patient was given approximately 10,000 units of penicillin every three hours, intravenously. Within twenty-four hours an astonishing improvement in the clinical condition was observed. There was a change from a comatose state to one of mental alertness, the temperature returned to normal and a blood culture taken at the end of the first day was negative. Improvement continued for a further period of forty-eight hours, but the supply of penicillin available was so limited that it was necessary to reduce the dose to 5,000 units every three hours. At the end of seventy-two hours of treatment there was a recurrence of fever, and a blood culture showed 20 colonies per cubic centimeter. The dose of penicillin was again increased to 10,000 units every three hours, and this was followed by a satisfactory improvement in the clinical condition. A negative blood culture was obtained a second time. However, after a further period of forty-eight hours the temperature again rose and successive blood cultures revealed an increasing number of colonies. It became obvious that the infection could not be controlled with the amount of penicillin available, and therapy was therefore discontinued.

In the second case of acute pneumococcic endocarditis, similar results were obtained. After the administration of 30,000 units of penicillin by infusion in the first two hours, followed by 10,000 units every four hours for three doses, a negative blood culture was obtained. A total of 175,000 units was given in the first three days and there was temporary improvement in the patient's condition. It became apparent, however, that the infection could not be controlled with the quantity of penicillin available, and therapy was discontinued.

In spite of the failure of penicillin as employed in these 2 fulminating cases of pneumococcic infection, it was felt that temporary sterilization of the blood stream in both instances represented a considerable achievement.

From these preliminary clinical trials it was apparent that, although penicillin was an extremely powerful bactericidal agent and essentially nontoxic, the amount of material necessary for systemic treatment was far greater than that which was available. A number of local infections, particularly staphylococcic infections of the eye,[3] were therefore chosen for topical treatment. Satisfactory results were obtained in several cases and additional evidence gained of the nonirritating nature of the penicillin preparations.

In the meantime the commercial preparation of penicillin under the auspices of the Office of Scientific Research and Development had progressed to the point where material was available for extended clinical trial. Since August 1942 limited quantities have been received through the Committee on Chemotherapeutic and Other Agents of the National Research Council. A general report on the study conducted under the auspices of this committee has recently been published.[4] The present communication is concerned with observations on the treatment of 100 cases which have been under the senior author's personal supervision.

SELECTION OF CASES FOR TREATMENT

Experimental work had clearly demonstrated that penicillin was primarily effective against gram positive organisms, both cocci and rods, and against gram negative cocci. It was further recognized that effective sulfonamide therapy was available for many infections caused by these organisms. Treatment was therefore largely restricted to those infections in which gram positive organisms and gram negative cocci played a dominant role and in which sulfonamide therapy was known to be ineffective. In addition a number of patients who exhibited definite sensitivity to the sulfonamides were treated as well as a few patients with profound anemia or renal insufficiency in whom sulfonamide therapy appeared to be unwise. As a result of these restrictions, staphylococcic infections constitute by far the largest single group in the present study. It should be emphasized, however, that the amount of penicillin necessary to kill staphylococci is considerably greater than that required for other pyogenic cocci. In general, gonococci and meningococci are the most sensitive, followed by pneumococci and hemolytic streptococci. Strains of Streptococcus viridans occupy a position comparable to that of staphylococci. It is therefore apparent that when penicillin becomes generally available its range of usefulness will be greatly extended.

ROUTE OF ADMINISTRATION

For systemic treatment the intramuscular route was chosen in the majority of cases. In the earlier part of the work a number of patients were treated intravenously, but except in very occasional circumstances this route was soon abandoned. It appeared to offer few advantages and several disadvantages. The advantages of the intramuscular route are that (1) a higher concentration is maintained for a longer period of time,[5] although the initial blood level is not so high as that obtained by intravenous administration, (2) the technic of the injections is simpler and can be carried out by a nurse or qualified attendant and (3) the injections are better tolerated by the patient. Occasionally patients complained of the local irritating effect of the intramuscular injection, but the degree of discomfort appeared to be associated with impurities in the product rather than with penicillin itself. With the better preparations the amount of discomfort experienced was minimal.

In instances of general sepsis it may be advisable to administer penicillin by continuous intravenous drip. Further work is required to determine whether the concentrations so achieved are more effective than those obtained by intramuscular injection.

For local treatment penicillin has been administered intrathecally, intrapleurally and intra-articularly. It has also been used for irrigation of sinus tracts and deep wounds and applied as dressings to superficial wounds. Solutions of penicillin have been applied directly to the eye in the form of baths, and relatively high concentrations have been obtained within the eye by iontophoresis.[6] In 1 case of acute laryngotracheitis in an infant, penicillin was instilled directly into a tracheotomy tube at frequent intervals with satisfactory results.

ABSORPTION AND EXCRETION

Our studies on the absorption and excretion of penicillin [5] are in general agreement with those reported by the Oxford workers and in greater detail by Rammelkamp and Keefer [7] and others. These studies show clearly that after intravenous injection penicillin disappears very rapidly from the circulating blood. Within fifteen minutes approximately 75 per cent of the injected material has disappeared and at the end of thirty minutes approximately 90 per cent. The remaining 10 per cent disappears slowly within the next three or four hours. After intramuscular injection the blood concentration rises rapidly, reaching a maximum within fifteen to thirty minutes, remains more or less stationary for the next half hour and then gradually falls off. At the end of three to four hours only traces can be detected in the blood. These observations indicate the advantages of intramuscular administration over intravenous.

After intrathecal administration penicillin has been demonstrated repeatedly in the spinal fluid at the end of twenty-four hours. The same has been shown to be true after both intra-articular and intrapleural administration.

Von Sallmann [8] of the Institute of Ophthalmology of the Presbyterian Hospital has shown that penicillin enters the aqueous humor of the normal eye in small concentrations within thirty-minutes after intramuscular injection. Moderate concentrations are obtained after

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This paper, in a symposium on "Antibiotic Agents," is published under the auspices of the Section on Experimental Medicine and Therapeutics.

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The clinical material for this study was obtained through the courtesy of the attending staffs of the affiliated units of the Columbia-Presbyterian Hospital Medical Center and other hospitals as well as private physicians.

The penicillin used in the preliminary phases of this study was prepared by Dr. Karl Meyer of the Institute of Ophthalmology, Presbyterian Hospital, from material supplied by Charles F. Pfizer and Company of New York. Since August 1942 all penicillin has been provided by the Committee on Medical Research of the Office of Scientific Research and Development under the supervision of the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council.

1. Chain, E.; Florey, H. W.; Gardner, A. C.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J., and Sanders, A. G.: Penicillin as a Chemotherapeutic Agent, Lancet **2**: 226 (Aug. 24) 1940.

2. Dawson, M. H.; Hobby, Gladys L.; Meyer, Karl, and Chaffee, Eleanor: Penicillin as a Chemotherapeutic Agent, J. Clin. Investigation **20**: 434 (July) 1941. Hobby, Gladys L.; Meyer, Karl, and Chaffee, Eleanor: Activity of Penicillin in Vitro: Observations on the Mechanism of Action of Penicillin; Chemotherapeutic Activity of Pencillin, Proc. Soc. Exper. Biol. & Med. **50**: 277, 281, 285 (June) 1942. Meyer, Karl; Chaffee, Eleanor; Hobby Gladys L.; Dawson, M. H.; Schwenk, Erwin, and Fleischer, G.: On Penicillin, Science **96**: 20 (July 3) 1942. Meyer, Karl; Hobby, Gladys L., and Chaffee, Eleanor: On Esters of Penicillin, ibid. **97**: 205 (Feb. 26) 1943. Hobby, Gladys L.; Meyer, Karl, and Dawson, M. H.: The Nature and Action of Penicillin, J. Bact. **45**: 65 (Jan.) 1943. Meyer, Karl; Hobby, Gladys L., and Dawson, M. H.: The Chemotherapeutic Effect of Esters of Penicillin, Proc. Soc. Exper. Biol. & Med. **53**: 100 (June) 1943. Dawson, Hobby, Meyer and Chaffee.[5]

3. These cases were treated by Dr. Philip Thygesson of the Institute of Ophthalmology with material prepared by Dr. Karl Meyer.

4. Keefer, C. S.; Blake, F. G.; Marshall, E. K.; Lockwood, J. S., and Wood, W. B.: Penicillin in the Treatment of Infections, a Report of 500 Cases, J. A. M. A. **122**: 1217 (Aug. 28) 1943.

5. Dawson, M. H.; Hobby, Gladys L.; Meyer, Karl, and Chaffee, Eleanor: Penicillin as a Chemotherapeutic Agent, Ann. Int. Med. **19**: 707 (Nov.) 1943.

6. von Sallmann, Ludwig: Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infection with Pneumococcus, Arch. Ophth. **30**: 426 (Oct.) 1943.

7. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.

8. von Sallmann, Ludwig, and Meyer, Karl: Penetration of Penicillin into the Eye, to be published.

9. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342 (March) 1943.

application of a cup bath to the eye for a period of five minutes, and relatively high concentrations are obtained by iontophoresis. Apparently a different situation exists in the cerebrospinal fluid.[9] In normal persons little or no penicillin is excreted in the cerebrospinal fluid, but in the presence of active inflammation of the meninges detectable amounts may be found.

It should be emphasized that the methods employed in studying the absorption and excretion of penicillin are necessarily rather crude. The selection of a procedure in which the killing power of blood, or other fluid containing penicillin, is determined against a test organism may give information of practical value in estimating the higher levels of drug desirable in that fluid but give no information regarding the biologic activity of material containing only traces of penicillin. There is reason to believe that this activity is very considerable and of great importance. For example, it can be readily shown that penicillin induces a profound change in the morphology and growth characteristics of hemolytic streptococci in dilutions as high as one part in one billion, far beyond the zone in which either bactericidal or bacteriostatic properties can be demonstrated. Further work is required to determine whether these changes are associated with changes in virulence of the infecting organism and whether they are of clinical significance.

DOSAGE

It was recognized from the beginning of the clinical trials that the establishment of correct dosage and frequency of administration were problems of great complexity. The early experimental work already indicated that different organisms varied greatly in their sensitivity, and more detailed study showed that even different strains of the same organism exhibited wide variations in their susceptibility. In general, strains of gonococcus and meningococcus were found to be most sensitive, followed by pneumococci, hemolytic streptococci (group A), Staphylococcus aureus, Streptococcus viridans, Staphylococcus albus and gram positive rods. Some strains of staphylococci were encountered which were highly resistant. As the work progressed it became the custom to test out the sensitivity of the infecting strain whenever possible. This procedure gives information of great value and is generally recommended, particularly in cases in which a satisfactory response has not been obtained. Details of the method used are being published elsewhere.

Early observations furthermore indicated that another important factor in determining appropriate dosage was the nature of the infection itself. Thus diffuse and phlegmonous lesions as a rule respond much more promptly than localized infections, although the activity of penicillin is not inhibited by pus or other exudates. This may be in large measure due to the actual concentration of the drug which can be attained at a given point. In any event, infections in well vascularized soft tissues respond to concentrations of drug that are apparently completely ineffective in relatively avascular hard tissues such as bone.

It should also be mentioned that little is as yet known concerning the minimal effective concentration for various types of infection. Such experimental work as has been done has been based on the assumption that effective concentrations should be constantly maintained in the circulating blood as is the custom in sulfonamide therapy. Certain facts suggest, however, that this may not always be necessary. Further work is required before any rigid schedule can be formulated, and in cases of doubt it is necessary to rely on the clinical response. In spite of these uncertainties and difficulties the following regimen is tentatively recommended as a result of the experience obtained in treating the present series of cases:

1. *Staphylococcic Infections.*—(*a*) Chronic osteomyelitis and chronic abscess formation, with or without bacteremia (in all such cases, sound surgical procedures should be adhered to and all foreign material, sequestrums and necrotic tissue cleanly removed by radical débridement), 20,000 units every four hours intramuscularly. Duration of treatment is dependent on the severity and extent of the process and on the clinical response.

Local treatment as indicated.

(*b*) Acute osteomyelitis, acute abscess formation, acute phlegmonous cellulitis and so on, 10,000-15,000 units every four hours intramuscularly. Seven days' treatment or less usually sufficient.

(*c*) Minor infections of the genitourinary tract (provided the infecting strain is sensitive), 10,000-15,000 units every four hours intramuscularly. If there is no clinical response in four or five days, continuation of therapy is probably not indicated.

(*d*) Empyema, meningitis or suppurative arthritis, 20,000 units locally daily or every two days for three or four injections. Systemic therapy as indicated by the nature of the primary infection.

2. *Pneumococcic Infections.*—(*a*) Pneumococcic pneumonia, 10,000 units every four hours intramuscularly. Ten injections frequently are sufficient, but continuation of therapy for two or three days may be necessary.

(*b*) Empyema, 20,000 units intrapleurally in 30 or 40 cc. of saline solution every two days for three or four injections. Systemic therapy as indicated.

(*c*) Meningitis, 20,000 units intrathecally daily. Two or three injections usually are sufficient. Systemic therapy as indicated.

3. *Streptococcic Infections.*—(*a*) Infections due to hemolytic streptococci (group A Lancefield), 10,000 units every four hours intramuscularly. Treatment for four or five days is usually adequate except in chronic infections, with or without bone involvement, when prolonged treatment may be necessary.

(*b*) Infections due to hemolytic streptococci other than group A and to Streptococcus viridans (information at present available is insufficient but strains of hemolytic streptococci belonging to groups B, C, D, E, F and G [Lancefield] have been found to be sensitive in vitro; some strains belonging to group D are resistant; strains of nonhemolytic streptococci are, as a rule, from two to four times more resistant than strains of group A hemolytic streptococci), 20,000 units every four hours intramuscularly. Duration of therapy is dependent on clinical response.

4. *Infections Due to Meningococci and Gonococci.*—(*a*) Blood stream infections and acute infections of the genitourinary tract, 10,000-15,000 units every four

hours intramuscularly. Two days' therapy is usually adequate. In cases of bacteremia, treatment should be continued for two days after the temperature has returned to normal.

(*b*) Meningitis, 20,000 units intrathecally daily. Two or three injections are usually sufficient. Systemic treatment as indicated.

(*c*) Acute arthritis, 10,000 units intra-articularly daily. Two or three injections are usually sufficient. Systemic therapy if intra-articular therapy is not possible.

5. *Mixed Infections.*—These are usually difficult to treat and relatively resistant. Dosage depends on a variety of factors: 20,000 units every four hours intramuscularly until a clinical response is obtained.

6. *Other Infections.*—Data available are insufficient.

7. *Topical Applications.*—Irrigation of sinus tracts or application of wet dressings daily with solution of penicillin containing 100 units per cubic centimeter are usually satisfactory.

Attention is called to three points in these tentative recommendations: 1. The initial dose recommended is the same as subsequent doses; there seems no valid reason for administering a large initial dose. 2. Higher doses are not recommended in the presence of bacteremia than in cases without bacteremia. In point of fact, the actual sterilization of the blood stream itself is in most instances a comparatively simple matter. 3. Except in general sepsis and for local therapy the intramuscular route is recommended for all injections. It will be apparent from the details of the cases subsequently reported that in many instances the dosage employed was smaller than that recommended in the foregoing schedule, which in itself is somewhat more conservative than that advocated in the recent report of the Committee on Chemotherapeutic and Other Agents.[4] Although the results were satisfactory in the majority of cases, the smaller doses were used in order to conserve the limited supply of penicillin. Probably a more prompt response would have been obtained in certain instances by the use of larger amounts of material. Further experience is required to determine the minimal effective dosage until such time as adequate supplies become generally available.

TABLE 1.—*Cases Treated Systemically*

I. Staphylococcic infections:		
(a) With bacteremia	18	
(b) Without bacteremia	19	
		37
II. Pneumococcic infections:		
(a) Pneumonia	10	
(b) Meningitis	4	
(c) Acute endocarditis	3	
(d) Empyema	2	
		19
III. Streptococcic infections:		
(a) Due to hemolytic streptococci	2	
(b) Due to nonhemolytic streptococci (other than subacute bacterial endocarditis)	2	
(c) Subacute bacterial endocarditis	10	
		14
IV. Meningococcic and gonococcic infections:		
(a) Meningococcic	2	
(b) Gonococcic	8	
		10
V. Mixed infections		14
VI. Infections of questionable causation		6
		100

METHOD OF ADMINISTRATION

Since the intramuscular route appears to be the route of choice except in certain types of infection, and since frequent administration is essential, it is desirable that the drug should be given in as small a volume as possible. The sodium salt is readily soluble in isotonic solution of sodium chloride and can be conveniently administered in amounts of 5,000 units per cubic centimeter. If larger doses are required, the concentration may be increased to 10,000 units per cubic centimeter.

In topical application the Committee on Chemotherapy has recommended solutions containing 250 or 500 units per cubic centimeter. From experimental observations and from our own clinical experience, solutions containing 100 units per cubic centimeter appear to be adequate in the majority of cases. However, no untoward effects have been observed from the use of concentrations far greater than those mentioned, and very possibly better results will be obtained by using stronger solutions.

PENICILLIN RESISTANT STRAINS

As previously mentioned, strains of staphylococci have been encountered which exhibit a high degree of resistance to penicillin. These have invariably been poor pigment producing strains of low virulence. So far, resistant strains of hemolytic streptococci (group A), pneumococci, gonbcocci or meningococci have not been encountered.

The acquisition of resistance to penicillin by virulent strains of various organisms, especially staphylococci, under both clinical and experimental conditions has been reported by several observers.[10] This is obviously a phenomenon of importance in prolonged therapy and has been advanced as an argument against the use of small dosage of the drug early in treatment. However, its significance seems to be greatly minimized by the further observation that in such instances there was a corresponding loss of virulence of the organism.[11] Furthermore, the acquisition of resistance to the drug must be a relatively rare event, since it was encountered in only 1 possible instance in the present series of cases, many of which were under treatment for prolonged periods.

GENERAL ANALYSIS OF CASES TREATED

Classified according to the nature of the infecting organism, the cases that have been treated systemically are summarized in table 1. No report is made at this time on cases treated topically.

CLINICAL RESULTS

1. *Staphylococcic Infections.*—The staphylococcic infections are divided into two groups, 18 cases with bacteremia and 19 cases without bacteremia, a total of 37 patients (tables 2 and 3).

(*a*) With Bacteremia (18 cases): The ages of the patients with bacteremia varied from 9 days to 74 years; 9 were over 40 years of age. The cases represented a wide variety of conditions, including 5 cases of proved acute osteomyelitis, and infection had persisted for variable periods of time before therapy was instituted. In 2 cases penicillin therapy was used in conjunction with surgical incision and drainage. In 15 of the 18 cases a satisfactory response was obtained; 3 cases relapsed but responded to subsequent therapy, 3 cases

terminated fatally and 1 case ended fatally because of a recurrence after an initial response. The 3 cases in which the outcome was fatal deserve special mention: 1. A 9 day infant with pyemia was inadequately treated for four days after the infection had assumed overwhelming proportions. (It will be observed, however, that a completely satisfactory result was obtained in another 18 day old infant with a more or less comparable type of infection which was much more intensively treated.) 2. In a case of epidural abscess and complete paraplegia the local and systemic infection was controlled but death occurred from complications associated with the paraplegia. 3. A patient with acute endocarditis and overwhelming sepsis was treated in the terminal stages of his illness. In the case in which death occurred after an initial response, multiple lung abscesses and bacteremia occurred in a two and a half month infant with cystic fibrosis of the pancreas. The blood stream infection was promptly controlled and the lung lesions gradually healed. Several weeks later, however, the pulmonary infection recurred and, because of difficulties inherent in the nature of the case, further treatment was not instituted. In summary, therefore, satisfactory results were obtained in all cases of staphylococcic bacteremia which could reasonably have been expected to respond. It is realized, of course, that a further follow-up period is required in many instances to determine the ultimate outcome.

Dosage.—The dosage employed in this group of cases varied from 5,000 units every four hours to 25,000 units every three hours. The total amount of penicillin given ranged from 180,000 units (excluding the infant which received only 20,000 units) to 2,250,000 units, and treatment lasted from five to thirty-two days. The wide variations in amounts of drugs administered were in part due to inexperience in the early stages and in part due to the meager supply of penicillin available at different times while the study was under way. Gradually with the accumulation of experience and with a more constant supply of material it became possible to work out a more rational schedule. Further experience is still required, however, before any rigid rules can be laid down, and different clinical conditions almost certainly require different amounts of drug. Examples of probably inadequate treatment are cases 1 and 3. In case 3, in which only 5,000 units was administered every three hours, the infection recurred twice and it was necessary to continue treatment for a total of sixteen days. Case 1, in which 10,000 units was administered every three hours, similarly regressed twice and was treated for a total of thirty days. Very possibly the infection could have been controlled in a shorter period of time had therapy been adequate. On the other hand, the infection in case 6, of desperate illness, in which 25,000 units was administered every three hours for nine days, might very possibly have responded to a smaller amount of drug. Probably the minimal adequate dosage lies somewhere between these two extremes.

From this limited series it is possible to draw the tentative conclusion that acute systemic infections and infections in well vascularized, soft tissues respond more promptly and require a smaller amount of drug than do more chronic infections, especially those in relatively avascular tissue, such as bone. In the former group 10,000 units every four hours would seem to constitute an adequate dose in most instances, while the latter require 20,000 to 25,000 units every four hours. The length of time for which treatment should be continued will vary according to the individual case, but

TABLE 2.—*Staphylococcic Infections With Bacteremia*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Osteomyelitis	74	10,000 q. 3 h. I. M.	30	2,250,000	Satisfactory	Patient with destruction of L4 and L5; infection recurred twice when therapy was interrupted; final outcome completely satisfactory
2	Osteomyelitis	12	5,000 q. 3 h. I. M.	8	190,000	Satisfactory	Dramatic response in an early acute case
3	Osteomyelitis	15	5,000 q. 3 h. I. M.	16	640,000	Satisfactory	Infection recurred twice; finally cured
4	Osteomyelitis	12	10-20,000 q. 4 h. I. M.	23	1,880,000	Satisfactory	Local infection recurred once when treatment was interrupted
5	Osteomyelitis, suppurative arthritis	12	10,000 q. 3 h. I. V. and I. M., 25,000 intra-articularly in one occasion	19	1,690,000	Satisfactory	Bacteremia and suppurative arthritis controlled; local infection persisted
6	Furuncle	14	5,000 q. 3 h. I. V.	5	180,000	Satisfactory	Blood culture became negative within 24 hours
7	Carbuncle, lung abscesses, pleural effusion	33	25,000 q. 3 h. I. M.	9	1,800,000	Satisfactory	A remarkable recovery in a desperately ill patient; carbuncle drained surgically
8	Perinephric abscess	28	5,000 q. 3 h. I. M.	11	440,000	Satisfactory	Acute infection following surgical drainage; response dramatic
9	Multiple lung abscesses	2½ mo.	2,500 q. 3 h. I. M.	32	602,000	Satisfactory	Infant with cystic fibrosis of pancreas; infection later recurred and patient succumbed
10	Epidural abscess, paraplegia	58	5,000 q. 3 h. I. M.	14	515,000	Died	Systemic and local infection controlled; death due to complications associated with paraplegia
11	Infected surgical wound	49	5,000 q. 3 h. I. V.	6	260,000	Satisfactory	Sulfonamides ineffective
12	Stomatitis, bronchopneumonia, and other conditions	18 days	2,500-5,000 q. 3 h. I. M.	16	495,000	Satisfactory	Sulfonamides ineffective
13	Traumatic urethritis, thrombophlebitis	58	5,000 q. 4 h. I. M.	18	575,000	Satisfactory	Sulfonamides ineffective
14	Pyemia	9 days	500 q. 3 h. I. M.	5	20,000	Died	Infant inadequately treated in terminal stages
15	Bacteremia of unknown origin	56	10,000 q. 3 h. I. M.	10	840,000	Satisfactory	Three positive blood cultures before treatment started; primary infection undetermined
16	Bacteremia of unknown origin, empyema	40	20,000 q. 4 h. I. M.	5	600,000	Satisfactory	Gratifying response in an acutely ill patient; systemic treatment only
17	Acute endocarditis, miliary abscesses and other conditions	73	20,000 q. 4 h. I. M. 1 day; 10,000 q. h. I. V. 2 days	3	480,000	Died	Overwhelming sepsis in a decompensated cardiac with diabetic gangrene
18	Suppurative bursitis	53	20,000 q. 4 h. I. M., local treatment for 10 days	7	600,000	Satisfactory	Severe infection involving entire upper arm treated in combination with surgery

a period of two days after the temperature has become normal would seem to be sufficient in most instances.

Four cases in this group which are of particular interest are briefly summarized:

1. A man aged 49 underwent a reconstruction operation for a probable pathologic fracture of the neck of the femur. The course was uneventful until ten days after operation, when the temperature began to rise. On the twelfth day the patient had a chill with a leukocytosis of 16,000. Inspection of the wound on the fourteenth day showed the presence of purulent material. Blood culture was positive for hemolytic Staphylococcus aureus. Local drainage was instituted and the patient started on sulfadiazine. The wound was opened widely and all sutures were removed. Despite maximal dosage of sulfadiazine and a combination of zinc peroxide and sulfadiazine locally, the patient continued to have elevated temperature with chills for the next four days and the blood culture remained positive. At this time intravenous penicillin 5,000 units every three hours intravenously was started. Forty-eight hours later the blood culture became negative and the temperature came down steadily, returning to normal six days after the beginning of penicillin therapy. Subsequent convalescence was uneventful.

2. A baby aged 18 days, who was said to have had thrush and a postnasal catarrh on discharge from a maternity hospital, was in acute distress on admission, cyanotic, with gasping respirations, and the mouth and nose were full of mucous secretion. A hemorrhagic membrane was present on the posterior pharynx. Nose and throat cultures were positive for hemolytic Staphylococcus aureus without monilias. Blood cultures were also positive for hemolytic Staphylococcus aureus. X-ray examinations revealed diffuse lobular pneumonia. The infant was placed in an oxygen tent and put on atropine and 1 per cent ephedrine nose drops. A 5 per cent solution of sodium sulfadiazine was given subcutaneously. On the sixth hospital day there was no significant improvement in spite of a sulfadiazine blood level of 13 mg. per hundred cubic centimeters. Penicillin was started, 5,000 units every three hours intramuscularly. Within twenty-four hours the baby began to show definite improvement and in succeeding days progress was rapid. The blood culture promptly became negative, the membrane of the mouth entirely disappeared and x-ray examinations during the third week revealed complete clearing of the lobular pneumonia.

3. A boy aged 12 years who had osteomyelitis with hemolytic Staphylococcus aureus septicemia was admitted with chills and fever of four days' duration and pain in the lower end of the femur. Three blood cultures were positive for hemolytic Staphylococcus aureus. Both sulfadiazine and sulfathiazole were administered without apparent effect. Penicillin therapy was instituted, 5,000 units every three hours intramuscularly. The temperature became essentially normal within two and a half days and no growth was obtained in blood cultures. Penicillin was discontinued after five days, and the patient made an uneventful recovery. X-ray examinations of the left femur two weeks later showed thickening of the cortex consistent with early involucrum formation of healing osteomyelitis.

4. A Negro aged 33 years was admitted to the hospital with the history of induration of the lower part of the scrotum for four days and sharp pain in the left lower anterior chest. The chest pain was aggravated by cough and deep respiration. On admission the patient was in acute distress and dyspneic, with a temperature of 104 F., a white blood cell count of 17,000 and pain in the left axillary region. There was a to and fro friction rub over the left lower chest with dulness on the right. The sputum was blood tinged. The perineal portion of the scrotum was swollen, with pus escaping from several sinus tracts. The patient was started on sulfathiazole 6 Gm. a day for two days, then sulfadiazine 6 Gm. a day for two days without response. Blood cultures were positive for hemolytic Staphylococcus aureus, and the clinical condition continued poor. Pleural effusion developed on the left and acute axillary pain on the right with an accompanying friction rub. X-ray examinations of the lungs revealed several areas suggesting early abscess formation. Penicillin therapy was instituted, 25,000 units every three hours intramuscularly. The temperature fell somewhat but remained at levels around 102 F. for five days. A thoracentesis was performed on the third day of penicillin therapy and thin purulent material obtained which grew hemolytic Staphylococcus aureus. The scrotal abscess was incised on the fourth day of penicillin therapy. The temperature continued to drop and reached normal levels on the tenth day, at which time penicillin was discontinued. The lesions in the lungs gradually resolved and the patient was discharged in good condition.

(*b*) Without Bacteremia (19 cases): The cases of staphylococcic infection without bacteremia represented an equally heterogeneous group and included 4 cases of chronic osteomyelitis. Satisfactory results were obtained in 15 of the 19 cases. Two of the unsatisfactory results occurred in cases of chronic osteomyelitis in which adequate surgery was not possible. It is of further interest that in 3 of the 4 unsuccessfully treated cases the infecting organism was subsequently found to be resistant to the action of penicillin in vitro. The first of these was a complicated case with avulsion of the foot, suppurative arthritis of the knee and osteomyelitis of the tibia and fibula. Adequate conservative surgery was not possible, and it was ultimately necessary to amputate the extremity. The other cases from which resistant organisms were cultured were those of chronic pyelitis and chronic cystitis respectively. In the former the infection was associated with recurring renal calculi over a period of years. The urine was temporarily sterilized, but the infection recurred when treatment was discontinued. The remaining case was one of chronic cystitis of four years' duration in which there was some doubt about the precise cause.

Dosage.—The comments with regard to dosage in cases of staphylococcic infection with bacteremia appear to be equally pertinent to cases without bacteremia. In simple soft tissue infections of an acute nature, 10,000 units every four hours would seem to be adequate. In many of the cases in the present series only 5,000 units every three hours was administered. Had larger doses been employed, the period of treatment could probably have been shortened. In chronic infections, especially those involving long bones, the situation is entirely different and much larger doses are indicated, from 20,000 to 25,000 units every three or four hours. Our experience in this type of case is limited, but Major Lyons of the Halloran General Hospital reports [12] that in such infections adequate surgery, with removal of all sequestrums, dead tissue and foreign material is absolutely essential. He recommends a dosage of 20,000 to 25,000 units every three or four hours for two days

10. McKee, C. M., and Houck, C. L.: Induced Resistance to Penicillin of Cultures of Staphylococci, Pneumococci and Streptococci, Proc. Soc. Exper. Biol. & Med. **53**: 33 (May) 1943. Schmidt, L. H., and Sesler, C. L.: Development of Resistance to Penicillin by Pneumococci, ibid. **52**: 353 (April) 1943.

11. McKee, C. M., and Houck, C. L.: Induced Penicillin Resistance in a Pneumococcus Type III Culture, Federation Proceedings **2**: 100 (March 16) 1943.

TABLE 3.—*Staphylococcic Infections Without Bacteremia*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Meningitis	14	5,000 q. 3 h. I. M.	13	500,000	Satisfactory	Meningitis following removal of brain tumor; patient subsequently died with ventricular block; no infection at autopsy
2	Suppurative parotitis	22	5,000 q. 3 h. I. M.	12	490,000	Satisfactory	Critically ill patient with profound anemia, jaundice, hematuria and nitrogen retention following sulfonamide therapy
3	Infected renal cyst	39	5,000 q. 3 h. I. M.	6	280,000	Satisfactory	Patient desperately ill; infected multilocular cyst of kidney ruptured when removed surgically; postoperative course satisfactory
4	Empyema	57	10,000 q. 3 h. I. M., 25,000 q. d. intrapleurally for 4 days	4	305,000	Satisfactory	Gratifying response without thoracotomy
5	Chronic osteomyelitis and suppurative arthritis	56	10,000 q. 3 h. I. M., 10,000 q. d. intraarticularly for 2 days	18	1,400,000	Unsatisfactory	Complicated case in which adequate surgery was not possible; infection temporarily controlled; therapy inadequate for a relatively resistant organism
6	Chronic osteomyelitis	22	10,000 q. 4 h. I. M.	8	400,000	Satisfactory	Adequate surgery
7	Chronic osteomyelitis	23	5,000 q. 3 h. I. M., 10,000 q. d. locally for 12 days	7	300,000	Unsatisfactory	Initial response satisfactory; further treatment with adequate surgery indicated
8	Suppurative arthritis	53	10,000 q. 3 h. I. M., 40,000 q. d. intraarticularly for 5 days	8	830,000	Satisfactory	Dramatic response
9	Furunculosis	69	5,000 q. 3 h. I. M.	3	125,000	Satisfactory	Recurring furunculosis of face and neck; prompt response
10	Furuncle	59	5,000 q. 3 h. I. M.	6	235,000	Satisfactory	Furuncle of nose; gradual response
11	Carbuncle	32	5,000 q. 3 h. I. M.	4	175,000	Satisfactory	Gradual response
12	Deep abscess, secondary to chronic osteomyelitis	52	5,000 q. 3 h. I. M., 2,000 q. 4 h. locally for 10 days	2	130,000	Satisfactory	Recurring abscess in a patient with chronic osteomyelitis; no recurrence in 12 months since treatment
13	Chronic cystitis	43	10,000 q. 6 h. I. M.	12	480,000	Unsatisfactory	Chronic bladder infection of 4 years' duration; etiology not clear
14	Postoperative infection	62	20,000 q. 4 h. I. M.	4	460,000	Satisfactory	Follow-up not obtainable
15	Postoperative infection	12	10,000 in 100 cc. saline q. d. locally	10	100,000	Satisfactory	Infected fascial transplant
16	Scalp infection	42	20,000 q. 4 h. I. M., local treatment for 10 days	2	240,000	Satisfactory	Scalp infection, in a patient with chronic dermatitis, following removal of brain tumor
17	Osteomyelitis	38	10-20,000 q. 4 h. I. M.	11	1,080,000	Satisfactory	Chronic osteomyelitis of 34 years' duration treated in combination with adequate surgery
18	Chronic pyelitis with recurring renal calculi	44	10,000 q. 4 h. I. M.	8	500,000	Unsatisfactory	Organism resistant in vitro
19	Wound infection	50	20,000 q. 4 h. I. M., local treatment for 10 days	2	240,000	Satisfactory	Widespread infection following laminectomy for inoperable cord tumor

prior to and for nine days subsequent to complete surgical debridement. He has further found that infections in long bones require larger doses than infections in flat bones.

Brief mention is made of 4 successfully treated cases in this group in which the results were particularly striking:

1. A youth aged 14 years had been operated on for brain tumor and was suffering from meningitis. The postoperative course was stormy, and on the eighth day spinal fluid cultures were positive for hemolytic Staphylococcus aureus. The same organism was recovered on two subsequent occasions. Adequate sulfonamide therapy did not influence the infection. Penicillin was administered, 5,000 units every three hours intramuscularly, and there was a gradual response. Treatment was continued for thirteen days, at the end of which time there was no clinical evidence of infection. The patient subsequently died with a ventricular block and at autopsy no evidence of residual infection was found.

2. A man aged 22 with suppurative parotitis and submaxillary cellulitis had been treated with sulfonamides for a streptococcic sore throat. Three days after the institution of sulfonamide therapy he began to vomit, became jaundiced and passed bloody urine for four days. On admission a large tense area of fluctuation presented in the region of the right parotid gland extending down the neck. The red blood cell count was 1,000,000, hemoglobin was 26 per cent and there was considerable nitrogen retention. The patient was desperately ill, and further sulfonamide therapy was obviously impossible. Surgical drainage, transfusions and penicillin 5,000 units every three hours intramuscularly were instituted. Cultures revealed hemolytic Staphylococcus aureus. A completely satisfactory response was obtained and, although a variety of treatments had been employed, the evidence strongly suggested that penicillin was primarily responsible for controlling the infection. In any event this case clearly demonstrates that penicillin may be safely administered when sulfonamides are contraindicated.

3. A patient with suppurative arthritis of the knee joint following arthrotomy for removal of synovia, medial meniscus and hypertrophic spurs had a normal postoperative course for seven days, when the knee began to be painful. On the ninth day the temperature spiked to 104 F. and the patient had a shaking chill. The knee was found to be grossly infected with hemolytic Staphylococcus aureus. Catheters were placed in the joint, and penicillin was administered both locally and intramuscularly. The patient was given 10,000 units every three hours intramuscularly and 2,500 units locally into catheters every three hours. The improvement was pronounced within twenty-four hours, and the subsequent course was completely satisfactory.

4. A woman aged 57, admitted because of empyema, had a cough of five days' duration and left chest pain. Adequate sulfadiazine treatment produced no response and the temperature continued around 101-103 F. with a white count of 32,000. Signs of fluid appeared over the left lung, and thoracentesis revealed thick pus swarming with hemolytic Staphylococcus aureus. Penicillin was instilled into the pleural cavity, 25,000 units daily for four days together with intramuscular injections of 10,000 units every three hours. At the end of this period the patient was moderately improved, but the temperature

12. Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army, J. A. M. A. **123**: 1007 (Dec. 18) 1943.

continued between 100 and 102 F. and the cultures were still positive, yielding a sparse growth of Staphylococcus aureus. Surgical intervention was contemplated but was withheld in view of the favorable clinical response. In succeeding days the patient continued to improve. The subsequent clinical course was satisfactory without surgical treatment.

2. *Pneumococcic Infections.*—The pneumococcic infections include 19 cases representing 10 examples of pneumonia, 4 of meningitis, 3 of acute endocarditis and 1 of empyema. In addition, 2 of the pneumonia patients had an infected pleural exudate representing probably an incipient empyema.

(*a*) Pneumonia: The results in pneumococcic pneumonia were satisfactory in all instances except 1, a case of overwhelming sepsis in a parturient female. In this case both the blood stream and the pleural fluid were found to be sterile twelve hours after therapy was started, but the patient died at the end of thirty hours, apparently of toxemia and general collapse. The sterilization of this patient's blood stream and pleural cavity within twelve hours demonstrates the remarkable bactericidal property of penicillin against pneumococci. In the remaining 8 cases the response was dramatic in 4, prompt in 2 and more gradual in the other 2. In general the results were satisfactory with doses of 10,000 units every four hours for one and a half to two days, but in 1 instance there was a dramatic response with a dose of 5,000 units every three hours for one and a half days.

(*b*) Meningitis: The 4 cases of pneumococcic meningitis all responded satisfactorily. In 2 of the 4, however, it was impossible to evaluate the role of penicillin because sulfonamides and antipneumococcus serum also were administered. In the third case the infection persisted in spite of adequate sulfadiazine therapy for twelve days. Penicillin was administered intrathecally, 20,000 units daily for three days, and systemic treatment instituted as well. Within twenty-four hours the temperature returned to normal, the spinal fluid became sterile and thereafter recovery was uneventful. The fourth case was complicated by the presence of mastoiditis and petrositis, and it was necessary to continue treatment for fifteen days before a satisfactory outcome was obtained. In this case also sulfonamides had proved completely ineffective. In 3 of the 4 cases of pneumococcic meningitis, penicillin was administered intrathecally as well as systemically; in 1 case systemic treatment alone was employed. It should be pointed out, however, that in this case the inflammation of the meninges may well have permitted the penicillin to traverse the blood brain barrier, which normally is resistant to its passage.[9]

The 4 cases of meningitis were treated from six to eighteen days, and the total dosage varied from 440,000 to 975,000 units.

(*c*) Acute Endocarditis: Reference has already been made to the 3 patients with acute pneumococcic endocarditis who were treated early in the course of the study. All received what was later recognized as totally inadequate dosage. All three succumbed to the infection, but in 2 instances the blood stream was temporarily sterilized, in 1 case on two occasions. In view of the small amounts of drug employed in such an overwhelming infection, the results at that time were considered encouraging. Since more adequate material has become available, the opportunity to treat such a case has not presented itself.

3. *Streptococcic Infections.*—(*a*) Due to Hemolytic Streptococci (Group A): At the present time there appears to be little indication for the use of penicillin in hemolytic streptococcus infections because of the scarcity of the material and because of the satisfactory response of the majority of such cases to sulfonamide therapy. Cases of sulfonamide intolerance are occasionally encountered and 2 such cases came under observation:

1. A woman aged 55 had suppurative arthritis of the right ankle following compound fracture dislocation. The fibula was plated and the dislocation reduced. Sulfadiazine was given and on the third day after operation the patient developed oliguria and hematuria with a blood urea nitrogen of 76 mg per hundred cubic centimeters. Sulfonamide therapy was discontinued but was later resumed after a return of kidney function. The first dressing on the thirteenth postoperative day showed that the wound was infected. The leg was put up in plaster, but the fever continued. Sulfonamides were again employed with gradually diminishing urinary output and no clinical improvement. After three months, amputation of the leg was considered. At this time the patient developed classic erysipelas of the face. Penicillin therapy was started, 10,000 units every three hours intramuscularly, and continued for one week. The result was dramatic. Within twenty-four hours the temperature returned to normal and subsequent convalescence was uneventful. At the end of one week the wound looked clean, no cellulitis was present and the area was covered with healthy granulations.

2. A woman aged 43 with a peritonsillar abscess and spreading cellulitis of the pharynx was unable to tolerate sulfonamides because of severe toxic reaction. Penicillin was administered, 10,000 units every three hours intramuscularly. There was satisfactory response and within forty-eight hours the infection had completely subsided.

(*b*) Due to Nonhemolytic Streptococci, not including cases of subacute bacterial endocarditis: Cases of this type of infection are only rarely encountered, and such a bacteriologic diagnosis should be made with care. Two patients were treated, both desperately ill in the terminal stages of their illness. In neither instance was the response satisfactory.

(*c*) Subacute Bacterial Endocarditis Due to Nonhemolytic Streptococci: This group of cases represents such a large and important problem that only certain aspects will be touched on in this communication; details will be published elsewhere. When penicillin was first discovered and its remarkable effect on gram positive organisms (including Streptococcus viridans) demonstrated in vitro, high hopes were entertained that it would be successful in combating this almost uniformly fatal type of infection. Despite the limited amount of material which has been available, the results herewith reported would appear in some measure to justify these hopes.

As previously stated, patients with this disease were selected for the preliminary clinical trials of penicillin. When larger amounts of material became available, 5 patients were treated as adequately as the still limited supply permitted. All 5 were classic examples of the disease with rheumatic hearts. In 2 of the 5 patients a satisfactory result was obtained and they are now living and well, thirteen and nine months respectively

after treatment was discontinued. The third patient, whose condition was particularly interesting, responded to penicillin on numerous occasions but invariably the infection recurred within two or three weeks after the discontinuance of treatment. This patient, however, is now in remarkably good general health and it is hoped that it will yet be possible to make a more intensive effort to terminate the infection. Of the 2 patients who were treated unsuccessfully, 1 received only 5,000 to 10,000 units every three hours for three interrupted periods of five days each; the other was intensively treated but succumbed to a cerebral embolus. At the time of death the blood culture was still positive. Much remains to be learned concerning the most effective method of administering penicillin in cases of subacute bacterial endocarditis, but these preliminary results appear sufficiently encouraging to justify an intensive study of the therapy of this disease as soon as adequate material becomes available.

4. *Gonococcic and Meningococcic Infections.*—(*a*) Infections Due to Gonococci: The number of cases of gonococcic infection treated is limited, but the results have been most instructive and satisfactory. Eight cases in all are reported, 6 of urethritis and 2 of arthritis. The 6 cases of urethritis were completely resistant to sulfonamide therapy.[13] All responded to penicillin and were cured from a clinical and bacteriologic standpoint within forty-eight hours. The dose was 10,000 or 15,000 units every three or four hours for two days.

The cases of arthritis were equally satisfactory. The first was a case of arthritis of the wrist with early destruction of the joint. Sulfonamide therapy and other measures had proved completely ineffective. The response to the administration of penicillin was unequivocal within forty-eight hours, and the final outcome was a normally functioning joint. The second case of arthritis was treated locally by the injection of 10,000 units daily for three days into the knee joint. The result was dramatic and the patient was discharged on the fifth day, all evidence of infection having subsided.

(*b*) Infections Due to Meningococci: Experience with meningococcic infections has also been very limited and includes only 2 cases. A satisfactory response was obtained in a patient who had developed anuria from sulfonamide therapy. This patient received 10,000 units intrathecally on two successive days and 10,000 units every three hours intramuscularly. There seemed to be no doubt that penicillin was responsible for controlling the infection. An unsatisfactory response was obtained in an infant aged 17 months who received only systemic treatment by intramuscular injections. The apparent failure of penicillin in this case lends further support to the finding that this agent does not normally pass through the blood brain barrier. The infection subsequently responded to antimeningococcus serum and sulfonamide therapy.

5. *Mixed Infections* (14 cases).—These cases represent a mixed group both bacteriologically and clinically and are difficult to discuss collectively. The majority were due to mixed infections of staphylococci and streptococci, but in several instances there was a multiplicity of other organisms including gram negative rods. As might have been expected, the results were the least satisfactory of the entire series. Eight of the 14 terminated fatally or gave unsatisfactory results. Almost cer-

13. Herrell, W. E.; Cook, E. N., and Thompson, Luther: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289 (May 29) 1943.

TABLE 4.—*Pneumococcic Infections*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Lobar pneumonia	40	5,000 q. 3 h. I. M.	3	115,000	Satisfactory	Recovery by lysis; type 25
2	Lobar pneumonia	45	10,000 q. 3 h. I. M.	1½	70,000	Satisfactory	Prompt response; type 7
3	Lobar pneumonia	47	10,000 q. 3 h. I. M.	2	160,000	Satisfactory	Dramatic response within 24 hours; type 7
4	Lobar pneumonia	43	5,000 q. 3 h. I. M.	1½	70,000	Satisfactory	Dramatic response within 12 hours; type 3
5	Lobar pneumonia	49	10-20,000 q. 3 h. I. M.	3	200,000	Satisfactory	Recovery by lysis; type 1
6	Lobar pneumonia	30	10,000 q. 3 h. I. M.	1	100,000	Died	Overwhelming sepsis in a parturient female; blood stream sterilized in 12 hours; death due to general toxemia; type 2
7	Lobar pneumonia	38	10-20,000 q. 4 h. I. M.	1	100,000	Satisfactory	Dramatic response in an apparently sulfonamide resistant case; type 3
8	Lobar pneumonia	22	10-20,000 q. 4 h. I. M.	1½	120,000	Satisfactory	Dramatic response; type 18
9	Incipient empyema following lobar pneumonia	47	20,000 intrapleurally	1	20,000	Questionable	Result difficult to evaluate; type 3
10	Lobar pneumonia, questionable empyema	67	10,000 q. 3 h. I. M., 30,000 intrapleurally	6	480,000	Satisfactory	Oliguria due to sulfonamides; cardiac; type 3
11	Bronchopneumonia	75	5-10,000 q. 3 h. I. M.	5	235,000	Satisfactory	Following prostatectomy; cardiac; type 8
12	Empyema	62	10,000 q. 3 h. I. M., 20,000 intrapleurally on five occasions	3½	375,000	Questionable	Empyema sterilized, thoracotomy to remove exudate; type 1
13	Meningitis, petrositis	37	10,000 q. 3 h. I. M.	15	975,000	Satisfactory	Gradual recovery; sulfonamides ineffective; mastoid drained surgically; type 3
14	Meningitis, mastoiditis	7 mo.	5,000 q. 3 h. I. V. or I. M., 5,000 q. d. intrathecally for 11 days	18	755,000	Recovered	Role of penicillin difficult to evaluate; also received sulfonamides and antipneumococcus serum; mastoid drained surgically; type 6
15	Meningitis, otitis media	5½ mo.	5,000 q. 3 h. I. M. or I. V., 1-5,000 q. d. intrathecally for 6 days	13	440,000	Recovered	Role of penicillin difficult to evaluate; also received sulfonamides and antipneumococcus serum; type 19
16	Meningitis	62	10,000 q. 3 h. I. M., 20,000 q. d. intrathecally for 4 days	6	440,000	Satisfactory	Dramatic response; sulfonamides ineffective; type 6
17	Acute endocarditis *	53	8,000 q. 3 h. I. V.	7	384,000	Died	Blood stream sterilized twice
18	Acute endocarditis *	48	15,000 q. 6 h. I. V.	3½	172,500	Died	Blood stream temporarily sterilized
19	Acute endocarditis,* meningitis	40	?	3	?	Died	An early case; dosage not measured in units

* These 3 cases were among the first cases treated; in the light of subsequent experience, totally inadequate amounts of the drug were given.

TABLE 5.—*Streptococcic Infections*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
			A. Due to Hemolytic Streptococci (Group A)				
1	Avulsion of foot, suppurative arthritis, erysipelas, cirrhosis of liver	55	10,000 q. 3 h. I. M.	8	650,000	Satisfactory	Oliguria and hematuria due to sulfonamides; amputation advised; response to penicillin dramatic
2	Peritonsillar abscess	43	10,000 q. 3 h. I. M.	4	310,000	Satisfactory	Sulfonamide sensitivity
			B. Due to Nonhemolytic Streptococci				
1	Pyemia	30	10,000 q. 3 h. I. M.	12	540,000	Died	Temporary improvement in a desperately ill patient treated in terminal stages
2	Meningitis, petrositis	5	5,000 intrathecally, 10,000 q. 3 h. I. M.	2	200,000	Died	Treated in terminal stages
			C Subacute Bacterial Endocarditis Due to Nonhemolytic Streptococci				
1-5	Subacute bacterial endocarditis		Preliminary clinical trials; dosage very small and not determined in units				No significant results
6	Subacute bacterial endocarditis	23	10-20,000 q. 3 h. I. M.	10	830,000	Recovered	Classic case; rheumatic heart; embolus to right femoral artery
7	Subacute bacterial endocarditis	27	5-10,000 q. 3 h. I. M.	23	1,420,000	Recovered	Classic case; rheumatic heart; embolus to right femoral artery and to left eye
8	Subacute bacterial endocarditis	40	10-40,000 q. 3 h. I. M.	30	6,670,000	Temporary improvement	Blood repeatedly sterilized; patient in excellent clinical condition after 9 months
9	Subacute bacterial endocarditis	28	5-10,000 q. 3 h. I. M.	17	975,000	Died	Temporary improvement only
10	Subacute bacterial endocarditis	23	10-20,000 q. 3 h. I. M.,	33	7,960,000	Died	Blood temporarily sterilized; death due to cerebral embolus; blood culture positive at time of death

TABLE 6.—*Gonococcic and Meningococcic Infections*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
			A. Due to Gonococci				
1	Acute arthritis of wrist	42	5,000 q. 3 h. I. M.	6	235,000	Satisfactory	Dramatic response in a sulfonamide resistant case
2	Acute arthritis of knee	41	10,000 q. d. intra-articularly	3	30,000	Satisfactory	Dramatic response with only local treatment
3	Urethritis	25	10,000 q. 3 h. I. M.	2	180,000	Satisfactory	Smears and cultures negative in 2 days
4	Urethritis	24	10-20,000 q. 4 h. I. M.	2	160,000	Satisfactory	Smears and cultures negative in 2 days
5	Urethritis	30	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
6	Urethritis	23	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
7	Urethritis	26	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
8	Urethritis	20	15,000 q. 4 h. I. M.	1½	150,000	Satisfactory	Smears and cultures negative in 2 days
			B. Due to Meningococci				
1	Meningitis	60	10,000 q. 3 h. I. M., 10,000 q. d. intrathecally for 2 days	3	240,000	Satisfactory	Anuria from sulfonamides
2	Meningitis	17 mo.	2,500-5,000 q. 3 h. I. M.	3	77,500	Unsatisfactory	Penicillin not given intrathecally; patient subsequently responded to sulfonamides and antimeningococcus serum

tainly therapy was inadequate in several instances but, on the other hand, in many cases it seemed doubtful that any type of therapy could have been successful. Four cases which responded satisfactorily in this group are briefly summarized:

1. An infant aged 3 months was acutely ill with laryngotracheitis. A tracheotomy was performed and cultures were positive for hemolytic streptococci, hemolytic Staphylococcus aureus and Streptococcus viridans. Penicillin was administered systemically, 600 units every three hours, and 1 cc. of a solution of penicillin containing 250 units per cubic centimeter was instilled into the tracheotomy tube every three hours. The following day the child seemed better and on the fourth day the temperature was normal. Thereafter recovery was uneventful.

2. A patient with aplastic anemia had fulminating Ludwig's angina due to hemolytic streptococci and hemolytic Staphylococcus aureus. The blood count showed only 800,000 red and 400 white cells and no kidney output. Three days of sulfadiazine therapy were without effect. Surgical intervention and tracheotomy were considered too hazardous. Penicillin was administered, 5,000 units every three hours intramuscularly. Within twenty-four hours the condition was definitely improved and within six days the neck had returned essentially to normal. However, the patient continued to pursue a downhill course, presumably because of cerebral bleeding associated with the aplastic anemia. At autopsy a few days later no gross evidence of infection was found in the tissues of the neck.

3. A man aged 36 with a comminuted compound fracture of the lower leg of ten days' duration was given sulfadiazine for four days without effect. Cultures yielded hemolytic Staphylococcus aureus and neisserian organisms. The patient was treated with penicillin locally, the solution being introduced through three catheters. The temperature dropped from levels of 101 and 102 to 99 and 100 F., and the wound became much cleaner. Penicillin was continued for six days, at the end of which time the temperature became normal and the wound continued to remain clean.

4. An infant aged 8 months had a lung abscess with cystic fibrosis of the pancreas. Blood cultures were positive for both hemolytic streptococcus and hemolytic Staphylococcus aureus. Penicillin 2,000 units was administered every three hours intramuscularly for fifteen days. The systemic infection was satisfactorily controlled and the lung lesion gradually disappeared.

TABLE 7.—*Mixed Infections*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Lung abscess	8 mo.	2,000 q. 3 h. I. M.	15	240,000	Satisfactory	Infant with cystic fibrosis of pancreas; blood culture positive for both hemolytic streptococcus and Staphylococcus aureus; remarkable response but infection recurred and infant died
2	Laryngotracheitis	3 mo.	600 q. 3 h. I. M., 250 q. 3 h. into tracheotomy tube	10	70,000	Satisfactory	Staphylococcus and streptococcus; tracheotomy ineffective
3	Ludwig's angina	60	5,000 q. 3 h. I. M.	7	295,000	Satisfactory	Staphylococcus and streptococcus; aplastic anemia; remarkable response
4	Acute tracheitis, pyemia	34	5-10,000 q. 3 h. I. M.	5	280,000	Died	Staphylococcus and streptococcus; treated in terminal stages
5	Bronchiectasis	56	10,000 q. 3 h. I. M.	3½	280,000	Unsatisfactory	No effect in a chronic case
6	Empyema	62	25,000 q. d. intrapleurally	3	75,000	Died	Putrid empyema; temporarily sterilized
7	Chronic cystitis	62	5,000 q. 6 h. I. M.	6	120,000	Unsatisfactory	Temporary improvement; mixed bacterial flora; anaerobic hemolytic streptococcus predominant
8	Necrotizing ulcer	58	5,000 q. 3 h. I. M., local penicillin dressings	3	120,000	Unsatisfactory	Staphylococcus and streptococcus; organisms resistant in vitro
9	Infected comminuted fracture	36	5,000 q. 3 h. locally by catheter	5	132,000	Satisfactory	Hemolytic Staph. aureus and Neisseriae
10	Lung abscess, metastatic brain abscess	46	10-15,000 q. 3 h. I. M. and I. V.; 20,000 intrapleurally on 8 occasions	50	4,050,000	Satisfactory	Lung abscess cleared; patient ultimately succumbed to brain abscess
11	Osteomyelitis, multiple sinuses, fecal fistula, etc.	57	10,000 q. 3 h. I. M.	8	620,000	Died	A very complicated case
12	Subphrenic abscess, empyema, suppurative pericarditis	29	10,000 q. 3 h. I. M., 50,000 intrapericardially	3	270,000	Died	A very complicated case
13	Cellulitis and multiple abscesses	44	25,000 q. 4 h. I. M., local penicillin dressings q. d. for 8 days	3	560,000	Satisfactory	Definite improvement in general and local condition
14	Necrotizing pharyngitis	7½	10,000 q. 4 h. I. M.	7	420,000	Satisfactory	Necrotizing pharyngitis in a patient with leukemia

TABLE 6.—*Infections of Uncertain Etiology*

No.	Clinical Diagnosis	Age	Penicillin: How Treated, Units	Penicillin: Days Treated	Penicillin: Total Dosage, Units	Result	Comment
1	Atypical pneumonia	56	10,000 q. 3 h. I. M.	4	300,000	Unsatisfactory	No response
2	Atypical pneumonia	23	20,000 q. 3 h. I. M.	3	480,000	Unsatisfactory	No response
3	Atypical pneumonia	48	10-20,000 q. 4 h. I. M.	3	270,000	Unsatisfactory	Questionable response
4	Bronchopneumonia	54	10-20,000 q. 4 h. I. M.	3	270,000	Died	Autopsy not obtained; postmortem cultures of blood, pleural exudate and aspirated lung all negative
5	Bronchopneumonia	4½	10,000 q. 4 h. I. M.	2	100,000	Satisfactory	Etiology obscure
6	Recurring parotitis (von Mikulicz's syndrome)	50	10,000 q. 3 h. I. M.	4	230,000	Unsatisfactory	No response

(Follow-up on this patient two months later showed a recurrence of the pulmonary infection and, in view of the uniformly fatal nature of this disease, further therapy was not employed.)

Only a few brief comments need to be made concerning the unsuccessful outcome in the remaining 8 cases of mixed infection. It has been clearly demonstrated experimentally that penicillin is not effective against gram negative bacilli. Furthermore, the English workers have shown [14] that certain gram negative rods including Escherichia coli actually secrete an enzyme, penicillinase, which destroys penicillin. It is therefore to be expected that the results would be unsatisfactory in cases of mixed infection when organisms of this type are present.

TOXICITY AND REACTIONS

A variety of experimental observations have indicated that penicillin is completely devoid of toxic effects in concentrations far beyond those necessary for therapeutic purposes. These observations have been fully borne out during the clinical trials. It should also be pointed out that the preparations of penicillin at present available are far from pure, the actual amount of pure penicillin being less than one fifth of the injected material. It is therefore possible that such reactions as may be observed may be due to impurities in the preparations or to associated factors attendant on the administration of the drug.

In the present series almost no complications or toxic effects have been observed. Three patients developed a mild urticaria. Chills and fever have not been observed since the early cases when the material was known to contain a pyrogenic substance. Thrombophlebitis, which has been reported by others,[4] has been observed in only 1 instance. This may be due to the fact that in our cases the intravenous route was employed only occasionally. Some patients complained of slight discomfort at the site of the intramuscular injections, but this type of reaction seemed to be connected with particular lots of material. In the great majority of cases no symptoms of any nature were observed.

Prolonged administration has not led to the development of any intolerance or sensitivity. One patient who had been treated intermittently with large doses for

more than six months experienced no delayed or cumulative effect of any type. The noteworthy fact has already been commented on that in this case the infecting strain showed no evidence of becoming resistant to the action of penicillin.

SUMMARY AND CONCLUSION

The present clinical study based on 100 cases demonstrates that penicillin is a remarkably effective agent in the treatment of infections due to staphylococci, pneumococci, streptococci, gonococci and meningococci.

The efficacy of penicillin in staphylococcic infections is of importance not because of a special sensitivity of staphylococci but because of the refractoriness of this type of infection to sulfonamide therapy.

A favorable response has been obtained in 15 out of 18 cases of staphylococcic bacteremia; in many instances the effect was dramatic. The 3 cases which terminated fatally all represented problems of great complexity.

The results in 19 cases of staphylococcic infection without bacteremia have been equally impressive. In 3 out of the 4 cases which failed to respond, the infecting organism was subsequently found to be resistant to penicillin in vitro. In chronic osteomyelitis the results have been satisfactory only when penicillin therapy was used in conjunction with adequate surgery. One case of frank empyema and 2 cases with heavily infected pleural exudate have been successfully treated without thoracotomy.

Penicillin has proved highly effective in the treatment of pneumococcic, hemolytic streptococcus, gonococcic and meningococcic infections. In this group 28 cases which failed to respond to sulfonamide therapy or in which sulfonamides were contraindicated have been treated.

TABLE 9.—*Summary of Results*

Type of Infection	No. of Cases	Satisfactory	Questionable	Unsatisfactory
Staphylococcic				
(a) With bacteremia	18	15	..	3*
(b) Without bacteremia	19	16	..	3*
Pneumococcic				
(a) Pneumonia	10	8	1	1*
(b) Meningitis	4	2	2	..
(c) Acute endocarditis	3	..	..	3*
(d) Empyema	2	..	2	..
Streptococcic				
(a) Due to hemolytic streptococci	2	2	..	..
(b) Due to nonhemolytic streptococci (other than subacute bacterial endocarditis)	2	..	..	2
(c) Subacute bacterial endocarditis	10	2	1	7*
Meningococcic and gonococcic				
(a) Meningococcic	2	1	..	1*
(b) Gonococcic	8	8	..	..
Mixed etiology	14	7	..	7
Questionable etiology	6	1	..	5
	100	62	6	32

* See text.

In 9 out of 10 cases of lobar pneumonia, 2 of which showed signs of incipient empyema, the results were uniformly good. The only failure occurred in an overwhelming infection in a parturient female. In this case the blood stream was sterilized within twelve hours, and death apparently resulted from general toxemia. One case of pneumococcic meningitis, which persisted in spite of intensive sulfonamide therapy, yielded promptly to the intrathecal administration of penicillin. The blood stream was temporarily sterilized in 2 cases of acute pneumococcic endocarditis treated with inadequate amounts of material early in the course of the study.

In sulfonamide resistant gonococcic infections, including gonococcic arthritis, the results have been particularly striking.

The response in 1 case of meningococcic meningitis in which penicillin was not administered intrathecally was unsatisfactory.

The results in the treatment of early cases of subacute bacterial endocarditis due to nonhemolytic streptococci have been encouraging.

In infections of mixed etiology the results have been less uniformly satisfactory. A favorable response has been obtained only in those cases in which gram positive organisms played a dominant role. Penicillin is not effective against gram negative bacilli.

Penicillin has proved ineffective in the treatment of 3 cases of primary atypical pneumonia.

The data at present available indicate that the most practical method of administering penicillin is by intramuscular injection at intervals of four hours. In the presence of severe sepsis intravenous administration may be necessary. Intrapleural and intra-articular administration have been employed with excellent results in cases of empyema and suppurative arthritis. In cases of meningitis, penicillin should be administered intrathecally.

Toxic reactions of a mild nature have been encountered only in occasional instances. Urticaria was observed in 3 cases and phlebothrombosis in 1. These reactions were probably due to impurities in certain preparations and not to penicillin itself.

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THE CLINICAL USE OF PENICILLIN

AN ANTIBACTERIAL AGENT OF BIOLOGIC ORIGIN

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At this stage of development of penicillin therapy it is a matter of extreme delicacy to formulate statements which may be considered final with regard to the clinical use of penicillin. It is further true that the treatment of infections with penicillin is accompanied by many problems not as a rule encountered in the use of therapeutic agents heretofore available.

It is well to recall that Fleming [1] in 1929 found that the broth in which Penicillium notatum had grown was inhibitory for certain pathogenic organisms. He named the substance penicillin. Unfortunately, penicillin did not receive clinical application for a period of eleven years following his observations. Penicillin, however, was used in the laboratory during this time for the purpose of isolating unsusceptible organisms. It is proper to award to Fleming the prize of priority for the first attempt to use penicillin in human subjects. He used broth filtrates to irrigate large infected surfaces of man and also irrigated the human conjunctiva

every four hours with this material. He reported only that no toxic effects were observed and did not report clinical results.

Following the isolation of an antibacterial agent, gramicidin, from Bacillus brevis by Dubos [2] in 1939, a reinvestigation of substances of biologic origin was naturally undertaken. Chain and other Oxford investigators [3] in 1940 reported on penicillin and its possibilities as a chemotherapeutic agent. One of the first reports on penicillin in America was that by Dawson and his associates [4] at the meeting of the American Society for Clinical Investigation in May 1941. In addition to studies on the antibacterial activity of penicillin, Dawson and his associates mentioned briefly its use in human infections. This report stimulated many investigators to attempt the preparation of penicillin and to study it further. In August 1941 the Oxford investigators [5] further reported on a fairly purified product of penicillin and included in this report the first clinical results. The experimental observations made at the Mayo Clinic on the antibacterial activity of penicillin were presented before the Society of American Bacteriologists in December 1941. Subsequent to this Heilman and I [6] were able to prepare and to obtain small quantities of pencillin for our investigations. In 1942 Heilman, Williams and I [7] reported observations on the clinical effectiveness of penicillin which were in agreement with the results published by the Oxford investigators. The report on penicillin in the treatment of infections published by Keefer and his associates [8] in August 1943 further confirmed the results published by the earlier investigators on the clinical use of this substance.

Penicillin has been used at the Mayo Clinic in the treatment of 62 patients suffering with bacterial infections.[9] A few of the cases have been reported previously; however, our clinical experience to date will be summarized in the present report.

PREPARATIONS OF PENICILLIN SUITABLE FOR CLINICAL USE

Sodium Salt of Penicillin.—Practically all of the experimental and clinical reports which have appeared previously in connection with the work on penicillin have had to do with studies in which the sodium salt of penicillin was used. The sodium salt of penicillin which my associates and I have used in our experimental and clinical studies was that prepared by the Abbott Laboratories. The sodium salt of penicillin is hygroscopic; it is destroyed easily by alterations of the hydrogen ion concentration in the surrounding medium and is sensitive to oxidizing agents. Heat, primary alcohols and metals alter the material. Because of these and other properties, the penicillin must be stored in the ice box at temperatures no higher than 5 C. This material is dispensed usually in sealed ampules and in as nearly the dry state as possible. The sodium salt of penicillin was used in 50 of the 62 cases on which this paper is based.

Calcium Salt of Penicillin.—The Oxford investigators in 1942 and again in 1943 [10] reported their observations on the calcium salt of penicillin. They found this to be nonhygroscopic and further reported that it could be handled more conveniently than the sodium salt. They made use of it for local therapy. It was their impression, however, that the calcium salt investigated by them was unsafe for intramuscular and intravenous use. Nichols and I [11] recently examined a calcium salt of penicillin (Winthrop) and reported experimental and clinical trials. The potency of this calcium salt investigated by us was 146 Oxford units per milligram and the salt contained 5.6 per cent of calcium. This material had been found by the manufacturer to be quite safe for subcutaneous and intravenous administration to mice.

Using the tissue culture method for the study of cytotoxicity of bactericidal agents which we [12] previously described, Heilman and I found that the calcium salt was somewhat less toxic for cellular elements than the sodium salt of penicillin now commonly used. The decrease of the radius of migration of lymphocytes from lymph node explants as compared with the controls was 13 per cent when the calcium salt was used in concentrations of 1 : 1,000, whereas the decrease of the radius of migration with the same concentration of sodium salt was 27 per cent. Further, the calcium salt appears to be relatively stable. In our laboratories we were unable to detect any loss of activity of the calcium salt in the dry state in sealed ampules which had been stored at room temperature for fifty-six days. The material was kept away from the light. Because of these and other observations, we felt that the calcium salt should prove safe for intravenous and intramuscular therapy. In 12 of the 62 cases included in this report the patients received the calcium salt of penicillin by the intravenous drip method employed at the Mayo Clinic. In order to determine any possible toxic effect from the intramuscular use of the calcium salt of penicillin, the following study was made: To patients not included in this report the calcium salt in amounts of 11,000 Oxford units in 10 cc. of isotonic solution of sodium chloride

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From the Division of Medicine, Mayo Clinic.

This paper, in a symposium on "Antibiotic Agents," is published under the auspices of the Section on Experimental Medicine and Therapeutics.

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was administered intramuscularly at three hour intervals. There was no evidence whatever of irritation of tissue.

DOSAGE AND METHODS OF ADMINISTRATION

Local Application.—The sodium and the calcium salt of penicillin as well as the broth filtrates containing penicillin are all satisfactory for local therapy. It appears from the reports now available that the calcium salt is superior to the sodium salt in this form of treatment. The reason is purely a question of stability and ease of handling of the material. The difference in the cytotoxicity of the two preparations is of no significance. Because many antibacterial agents of similar potency are easily available for local therapy, we have not felt justified in using the limited amounts of penicillin available for this purpose. Sulfonamide therapy has proved very satisfactory for the local treatment of bacterial infections. Other agents, such as gramicidin and the synthetic quaternary ammonium compounds, are also very satisfactory. The compounds just mentioned are far more stable than penicillin, and their preparation is not accompanied by the complex problems associated with the production of penicillin. We therefore have used penicillin locally in only 2 cases. The results were satisfactory.

Intramuscular Administration.—No doubt repeated intramuscular injection of penicillin in doses of 10,000 to 20,000 Oxford units dissolved in 5 or 10 cc. of isotonic solution of sodium chloride or distilled water is reliable. Nevertheless this method has some disadvantages. Because penicillin disappears from the blood stream rather rapidly, this method of administration requires repeated injections of the material at three or four hour intervals throughout the entire twenty-four hours. This requires considerable time on the part of medical personnel. Further, if 20,000 units is administered every three hours in this fashion, the total daily dose will be 160,000 Oxford units per patient. This amount of penicillin in our experience is far in excess of that required to obtain satisfactory results in the treatment of infections, including septicemia. Therefore, in order to conserve the limited amount of penicillin available, we have used the intramuscular method of administration in only those cases in which the intravenous drip method was not feasible. Two patients were treated by means of the intramuscular method. One was an infant 10 days of age suffering with staphylococcic septicemia (120 colonies per cubic centimeter of blood). The patient recovered. The second patient was an infant 6 months of age suffering with extensive facial and orbital cellulitis due to Staphylococcus aureus. Suitable veins were not available to permit the use of the intravenous drip administration. The patient recovered.

Intravenous Administration.—Two methods of intravenous administration are possible. Penicillin in concentrated solutions (10,000 Oxford units per 10 cc.) administered every two or three hours has been advocated by some. This results in a daily dose of 80,000 to 120,000 units. This method is subject to the same disadvantages mentioned in the discussion of the interrupted intramuscular method of administration. Larger doses and repeated venipunctures are required, although satisfactory clinical responses may indeed be obtained.

If the interval between the repeated intravenous injections is longer than two hours, it is important to remember that there will be a period during which little or no penicillin is present in the blood. This in my opinion is undesirable, especially in the treatment of infections of the blood stream. In my experience the continuous or nearly continuous intravenous administration of pyrogen free penicillin is the most suitable method. For the treatment of moderately severe or severe infections 40,000 Oxford units per twenty-four hours has been found to be an adequate daily dose of penicillin. Half of the twenty-four hour dose is dissolved in 1 liter of isotonic solution of sodium chloride. The material may be administered in a 5 per cent solution of dextrose in triple distilled water; however, continuous administration of dextrose may produce venous irritation at times. We therefore administer the material in dextrose only in those cases in which the use of sodium chloride is undesirable. Initially, between 100 and 200 cc. of the material is administered at a fairly rapid rate. Following this the rate of injection is regulated to between 30 and 40 drops per minute. The second liter containing penicillin is attached to the continuous intravenous system eight to ten hours later. Repeated venipunctures are avoided by allowing saline or dextrose solution to drip in slowly during the interval in which, for any reason, the subsequent penicillin has not been delivered to the patient's room. An 18 gage Lewisohn transfusion needle is inserted deeply into the vein and anchored with adhesive plaster. A simple arm splint is applied to keep the arm in position. This is tolerated well by the patient and renders this method of administration possible and not uncomfortable. Some patients receiving penicillin in this fashion may be allowed to sit up at times during the course of the therapy. It has been possible to administer penicillin without changing the needle or disturbing the apparatus for a period as long as eight days.

Intrathecal Administration.—Rammelkamp and Keefer [13] made the interesting observation that penicillin could not be detected in the spinal fluid following intravenous administration of the drug to normal subjects. Nichols and I [14] made observations which confirm their findings. We administered as much as 30,000 units of penicillin intravenously in a period of fifteen minutes to a patient who did not have any demonstrable lesions of the central nervous system, and we could not detect any penicillin in the spinal fluid removed thirty and sixty minutes after the intravenous injection. We have not determined whether or not the same finding obtains in diseases which involve the cerebrospinal apparatus, such as meningitis. At the moment, therefore, it seems advisable to supplement

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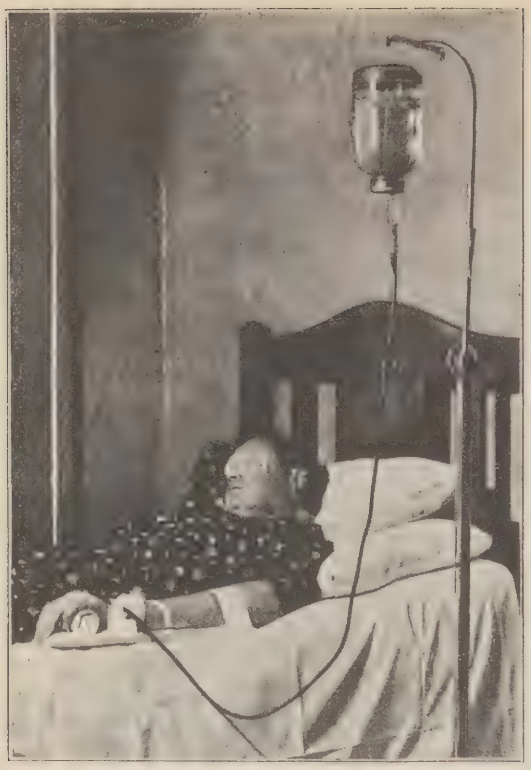

Fig. 1.—Administration of penicillin by the continuous intravenous drip method with patient recumbent. The patient represented received penicillin in this manner for eight days without withdrawal of the needle. He could move about with the needle in place.

intravenous therapy by intrathecal administration of 5,000 to 10,000 Oxford units of penicillin once daily to patients under treatment for meningitis.

Dosage.—Only on two occasions in the treatment of 62 patients have we found it necessary to use more than 40,000 units per day. These two patients received between 40,000 and 60,000 units for one or two days, but in no instance has the daily dose exceeded this amount. It appears that the cases were fairly representative of the moderately severe and severe bacterial infections usually encountered. For example, 16 patients were suffering with septicemia, and the blood cultures of all were positive before treatment.

METHODS OF STANDARDIZING PENICILLIN

The commonly used methods for the standardization of penicillin have been reviewed by Foster and Woodruff.[15] They discussed the principles, the merits and the disadvantages of the different bacteriologic methods now used. They pointed out that the serial dilution methods are wanting in accuracy and advocated a modified broth method devised in their laboratory. The turbidimetric method of Foster used by some is rather difficult for routine purposes. Probably the most commonly used method of assay of penicillin is that described by Abraham and his associates [5] and is known as the Oxford method. The unit is that amount of penicillin which under the conditions of the assay gives an inhibition zone 24 mm. in diameter. The unit also may be expressed as that amount of penicillin which regularly inhibits the growth of a known inoculum of the test organism. The test organism used by the Oxford investigators was Staphylococcus aureus.

Heilman [16] has stated that one of the chief hazards in the methods commonly used is the maintenance of a suitable standard. Using the tissue culture technic, she has devised a method of titrating penicillin which does not require the use of a standard in the performance of the test. This method, which compares favorably with the Oxford method, is the one used in our laboratories for the titration of samples of penicillin. Unless one is interested in some particular problem of a research nature, it is not necessary in my opinion to know the penicillin content of the blood of a patient under treatment. When amounts of penicillin are detectable in the blood by the commonly used methods, the penicillin present is certainly in excess of the ordinary therapeutic requirements. The method described by Heilman is not suitable for the determination of the amounts of penicillin present in the blood and tissues. Her method has been found entirely satisfactory, however, for the determination of the potency of penicillin to be administered therapeutically. Since there is often a discrepancy between the estimated strength of a

Fig. 2.—Administration with patient sitting.

13. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425-437 (May) 1943.

14. Nichols, D. R., and Herrell, W. E.: Unpublished data.

15. Foster, J. W., and Woodruff, H. B.: Microbiological Aspects of Penicillin: I. Methods of Assay, J. Bact. **46**: 187-202 (Aug.) 1943.

product at the time of its preparation and the actual strength at the time of its use, one should be prepared to titrate from time to time penicillin to be used clinically. This discrepancy between the estimated and the actual strength of the product is completely understandable in view of the great lability of the product. I am in complete agreement with Heilman that, because of the scarcity of penicillin, it is most important not to use more of it than is necessary. It is likewise most important to use enough. To be able to determine the strength of a preparation of penicillin at the time it is being administered is therefore essential and is the crux of the whole matter.

ANALYSIS OF SIXTY-TWO CASES

Penicillin has been used in the treatment of 62 patients suffering from various bacterial infections. As previously mentioned, in 50 cases the sodium salt and in 12 the calcium salt of penicillin was administered. Penicillin was used locally in only 2 instances. Because of the lack of suitable veins for administration by continuous intravenous drip, penicillin was administered by repeated intramuscular injection in 2 cases. In the remaining 58 cases penicillin was administered by the intravenous drip method previously described. The causative organisms isolated in these 62 cases and the results obtained from penicillin therapy are contained in table 1. The diagnosis in each of the separate groups and the results will be discussed separately.

Staphylococcus Aureus Infections.—In 28 cases Staphylococcus aureus was the organism isolated. Fourteen of the 28 staphylococcic infections were examples of staphylococcic septicemia, in all of which positive blood cultures were obtained before treatment. The results of treatment in the 14 cases of septicemia will be discussed separately. In the remaining 14 cases the blood cultures were negative, but in all but 2 the infections were acute, severe localized staphylococcic infections. The results were entirely satisfactory in 22 of the 28 cases. The result was doubtful in 2, and failure occurred in 4, 2 of which were examples of septicemia associated with clinical evidence of a valvular cardiac lesion at the time the treatment was begun.

The clinical diagnoses in these cases were as follows: extensive cellulitis of the face (Ludwig's) or the extremities in 16, infections of the urinary tract in 5, postoperative infection of a wound in 3, osteomyelitis in 2, cellulitis of the thoracic wall in 1 and chronic ulcer in 1.

Injection with Neisseria Gonorrhoeae.—Since the first report from the Mayo Clinic by Cook, Thompson and myself [17] on the experimental and clinical effectiveness of penicillin in the treatment of gonorrheal infection resistant to sulfonamide compounds, further clinical experience indicates that penicillin is highly effective in this condition. Cook, Pool and Herrell [18] have reported the results in detail. Penicillin has been used in a total of 16 cases. In no instance did failure occur. The duration of treatment is seldom more than forty-eight to seventy-two hours. It is never necessary to use more than 100,000 to 150,000 Oxford units of penicillin in these cases. Complete cures have been obtained by using as little as 65,000 units. The intramuscular administration of penicillin is probably quite well adapted to this type of case. On the other hand, we have used the intravenous drip method, which permits a longer period of treatment than is possible with the same amount of penicillin usually necessary for a twenty-four hour course of intramuscular injections. This seems desirable since we continue treatment to the time when the first negative cultures have been reported.

TABLE 1.—*Organism—Results of Treatment with Penicillin in Cases of Acute Localized Infection*

Organism Isolated	Cases	Result		
		Recovery Satisfactory	Doubtful	Failure
Staphylococcus aureus	28	22	2	4
Neisseria gonorrhoeae	16	16	..	..
Streptococci				
Hemolytic	3	2	..	1
Anaerobic	4	4	..	..
Nonhemolytic	3	1	..	2
Actinomyces bovis	4	2	..	2
Micrococcus	2	..	1	1
No organism	2	1	..	1
Total	62	48	3*	11*

* Five of the eleven results listed as failures and one of those listed as doubtful occurred in cases of acute or subacute bacterial endocarditis.

Streptococcic Infections.—Because of the effectiveness of the sulfonamide compounds against hemolytic streptococcic infections, we did not find it necessary to use penicillin in more than 3 cases of this type. In the first instance the diagnosis was multiple hepatic abscesses; the result was unsatisfactory. In the second the diagnosis was extensive cellulitis of the face (Ludwig's) without bacteremia, and in the third the diagnosis was extensive cellulitis of the face with septicemia. Both the patients with cellulitis recovered.

A partially or completely anaerobic streptococcus was isolated in 4 cases. Three of the patients were suffering with osteomyelitis. One had postoperative septicemia. Satisfactory results were obtained in all 4 instances.

There were 3 cases in which a nonhemolytic streptococcus was the organism isolated. In 2 instances the diagnosis was subacute bacterial endocarditis. In both of these the treatment resulted in failure. In 1 instance the diagnosis was extensive cellulitis of the mouth and tongue; the patient recovered.

Miscellaneous Infections.—In 4 cases actinomycosis was treated with penicillin. In 1 instance the infection was abdominal actinomycosis complicated by carcinoma of the colon; the result was unsatisfactory. In 3 instances the diagnosis was maxillofacial actinomycosis. There were one failure and two recoveries.

16. Heilman, Dorothy H.: Unpublished data.

17. Herrell, W. E.; Cook, E. N., and Thompson, Luther: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289-292 (May 29) 1943.

18. Cook, E. N.; Pool, T. L., and Herrell, W. E.: Further Observations on Penicillin in Sulfonamide Resistant Gonorrhea, Proc. Staff Meet., Mayo Clin. **18**: 433-437 (Nov. 17) 1943.

In 2 cases a micrococcus was isolated repeatedly from the blood on culture, and both patients were suffering with subacute bacterial endocarditis. The treatment with penicillin was ineffective in 1 patient. The other patient is still living and in spite of the presence of endocarditis the blood cultures are negative. The result is listed as doubtful.

In 1 case an overwhelming gas gangrene infection was present. The patient died before bacteriologic studies could be made and before completion of intravenous administration of 1 liter of saline solution containing 20,000 units of penicillin.

TABLE 2.—*Results of Penicillin Therapy in Cases of Septicemia*

Organism Isolated	Cases	Recovery	Failure
Staphylococcus aureus	14	12	2
Hemolytic streptococcus	1	1	—
Anaerobic streptococcus	1	1	—
Total	16	14 (88%)	2 (12%)

In another case in this series positive bacteriologic results could not be obtained before penicillin was administered. However, the patient was suffering with extensive cellulitis of the face and mouth (Ludwig's). The patient received 240,000 units of penicillin by the intravenous drip method over a nine day period. This patient recovered.

The Question of Surgical Drainage.—On excluding the 16 cases of gonorrhea in which treatment with penicillin was given because the infection was resistant to sulfonamide compounds, there remain 46 instances of infection caused by other pathogenic bacteria. In some of these 46 cases, the infection localized and was susceptible of drainage; however, in only 10 such cases was drainage instituted. Even some of these 10 patients, I believe, would have recovered without drainage.

PENICILLIN IN THE TREATMENT OF BACTEREMIA

Since bacteremia or septicemia constitutes a most serious problem in the treatment of infections, it is appropriate to analyze thoroughly the results that followed the use of penicillin in these cases. In nearly every instance one or more of the sulfonamide preparations had been administered without demonstrable benefit. Included in this group were all the patients whose blood cultures were positive before or at the time of institution of penicillin therapy. The blood cultures in 20 of the 62 cases included in this report were positive.

Four of these cases were examples of subacute bacterial endocarditis, and in spite of temporary sterilization of the blood stream following the administration of penicillin we cannot report at this time a single recovery. These 4 cases are therefore excluded henceforth in the discussion of the results in bacteremia.

In 14 of the 16 cases of septicemia (table 2) the organism isolated from the blood was Staphylococcus aureus. Hemolytic streptococci were isolated in one and anaerobic streptococci in another. Fourteen of the 16 patients suffering with septicemia recovered; 2 died. It is significant that the 2 patients who failed to recover had definite clinical evidence of a possible valvular cardiac lesion at the time penicillin therapy was instituted.

One of these patients was a woman aged 31 who was admitted after having been under treatment with sulfonamide therapy for eighteen days because of staphylococcic septicemia which apparently started from an abscess in the hand. At the time of her admission her blood cultures were negative, and penicillin was not administered. Several days after admission she was delivered of a normal but premature child. At the time of her admission a definite cardiac murmur was present and there were other physical manifestations suggestive of acute endocarditis. At the onset of labor a highly septic fever developed, and blood cultures revealed forty-five colonies of Staphylococcus aureus per cubic centimeter. Subsequent to this penicillin therapy was instituted, but the patient failed to respond favorably and died after three days of treatment. Necropsy revealed acute mitral bacterial endocarditis with multiple abscesses throughout most of the viscera.

The second patient who failed to recover was a man aged 64 under observation for a severe infection of the urinary tract due to Staphylococcus aureus. A positive blood culture for Staphylococcus aureus was obtained on the fourth day after his admission. On the fifth day penicillin therapy was started. At the time penicillin therapy was begun a definite systolic murmur could be heard, and a diagnosis of possible acute endocarditis was made. After receiving 30,000 units of penicillin by the intravenous drip method, the patient died. He had been treated for only a little more than twelve hours. Necropsy revealed acute vegetative endocarditis and multiple abscesses in both kidneys.

It seems likely that both of these patients were suffering with acute vegetative endocarditis at the time penicillin therapy was initiated. In our experience vegetative endocarditis has not developed during treatment with penicillin. Although this group of cases of septicemia is small, it is gratifying to experience recovery of 14 of 16 patients suffering with such a severe infection (recovery rate 88 per cent).

The daily dose of penicillin administered in these cases has been, as a rule, between 30,000 and 40,000 units in twenty-four hours. In the cases of septicemia the total amount of penicillin administered by the intravenous drip method varied between a minimum of 160,000 units and a maximum of 473,000 units. The average duration of treatment of the patients suffering from septicemia was ten and a half days. It is our practice to continue the administration of penicillin until two successive negative blood cultures have been obtained and the temperature has reached normal.

The age of the patient does not appear to be of any prognostic significance under adequate penicillin therapy. The youngest patient treated for septicemia was a child 10 days of age. The oldest patient was 75 years of age. It seems reasonable to assume that satisfactory results can be obtained by using the daily dosage recommended and administering the material by the intravenous drip method. This permits penicillin to be delivered into the blood stream continuously or nearly so, a very desirable factor in the treatment of patients with bacterial infections, especially those whose blood cultures are positive. The average total amount of penicillin used per patient for severe infections is slightly

less than 300,000 units. It seems unnecessary to use more if satisfactory results can be obtained with this amount administered by the method advocated.

TOXIC REACTIONS

Chills and Fever.—Chills and fever have been reported by other investigators. All of the material used in our work has been pyrogen free penicillin. In no instance have we observed this reaction.

Thrombophlebitis.—We observed a mild venous irritation in 3 of the 62 cases reported. In all 3 instances this reaction promptly subsided after the intravenous drip had been changed to another site. It is interesting that this occurred only in cases in which penicillin was being administered in a 5 per cent solution of dextrose. Prolonged administration of dextrose itself may result in irritation of veins in some instances. Stronger solutions of penicillin than we have used may be responsible for some of the phlebitis reported to result from penicillin therapy. It is quite possible also that substances introduced in the processing of penicillin, if still present in the final product, may explain this reaction. I am not prepared to state with certainty that the possibilities just mentioned are the true factors involved in "penicillin phlebitis." Certainly the reaction has not been at all troublesome in our experience.

SUMMARY AND CONCLUSIONS

It is apparent that penicillin is a highly effective antibacterial agent against susceptible pathogens. Among the cases in which penicillin was used were infections due to Staphylococcus aureus, Neisseria gonorrhoeae, streptococci, actinomycetes and micrococci. Satisfactory results were obtained in 48 of the 62 cases. The results were doubtful in 3, and failure or death occurred in 11 instances, in 5 of which the condition was acute or subacute bacterial endocarditis. If the latter 5 cases are excluded, the cases in which the results were satisfactory would number 48 of 57 (84 per cent).

Both the sodium and the calcium salt of penicillin have been used in the treatment of the bacterial infections reported. Either of these salts may be applied locally or administered intravenously or intramuscularly. The calcium salt appears to be the more stable.

The experience in this group of cases seems to justify the conclusion that 40,000 units of penicillin per day is sufficient in the treatment of the infections described. In our hands the intravenous drip method of administering penicillin has been the most satisfactory. In some instances intermittent intramuscular administration may be equally satisfactory. However, if experience proves that larger doses are required for the intermittent intramuscular method than for the intravenous drip method, the former is not the one of choice at the present time. Penicillin should be reserved so far as possible for infections resistant to sulfonamide compounds. Penicillin therapy is no substitute for sound medical and surgical judgment in the treatment of bacterial infections.

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THE CLINICAL USE OF PENICILLIN

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In August 1943 penicillin supplied by the Office of Scientific Research and Development was made available, through the Committee on Chemotherapeutic and Other Agents [1] of the National Research Council, for clinical investigations at Stanford University Hospital. The ensuing report largely concerns our experiences with penicillin, with reference especially to continuous subcutaneous and intravenous infusions, since the subcutaneous and intravenous routes have not been extensively used by most investigators.

Penicillin has been furnished to us as the sodium salt. This is a brown or yellow powder, put up in sealed glass ampules, which is extremely soluble in water and in saline or dextrose solution; 10,000 units or more is readily taken up in 1 cc. of fluid. The material is unstable in the air and very hygroscopic; its potency is impaired by heat and in acid mediums.[2] Therefore the sealed ampules must be preserved in the refrigerator until used; however, a day's dose, made up in the proper solution, may safely be kept in the cold. Various lots of the sodium salt of penicillin have differed greatly in color when dissolved. The earlier batches especially yielded intensely yellow or even brownish solutions. The material more recently received has been almost colorless. It is our impression that these pale solutions contain less of certain impurities which may be associated with clinical reactions (see the following section).

The exact constitution of penicillin has not yet been worked out. Hence the material cannot be standardized by chemical means but is assayed by its biologic effect. The clumsy Florey (Oxford) unit—the amount of penicillin compared with an arbitrary standard which completely inhibits the growth of a test strain of Staphylococcus aureus—is still used and probably will hold its place until a chemically standardized product is available. In Florey's original material there were 40 to 50 units per milligram [3]; material which runs 700 to 1,000 units per milligram has now been prepared. Most of our material for which unitage was stated had a potency of about 300 units per milligram. A few other points should be kept in mind: first that penicillin, in large part at least, exercises a direct bactericidal action; second, that some preparations have immense potency and are effective in dilutions of over 1 to 100,000,000.

Those who have not actually worked with penicillin may have the idea that its use is a simple matter. This is not at all the case. We soon found that the patients should be housed in one physical unit and that a special "penicillin team" was necessary in order to carry out the treatments effectively. The duties of this team have been:

1. To answer numerous calls and to interview physicians desiring to send patients for penicillin therapy in regard to the

suitability of these prospects.

2. To make preliminary examinations (physical and bacteriologic) in order to identify the infection and to establish proper records.

3. To plan the dosage and the route of penicillin therapy and to organize any ancillary treatment necessary in cooperation with surgeons, orthopedic physicians and other specialists.

4. To make up the total daily dose of penicillin for each patient in the desired amount and in the proper solvent. To keep records of the commercial lot used for each patient. To decide when treatment should be stopped.

5. To set up infusion sets and introduce needles for subcutaneous and for intravenous flow. To supervise the apparatus and see that it functions properly day and night.

6. To follow the clinical course and bacteriologic findings and plan therapy from day to day.

7. To measure blood levels of penicillin and the urinary excretion of the substance.

8. To keep and compile adequate records and to follow patients as long as necessary after treatment.

When 4 to 7 sick persons were under treatment at the same time the team found that they had their hands full. It is our feeling that at present best results will not be obtained by the occasional treatment of a single patient by a doctor not fully "at home" with the problems of penicillin therapy.

ROUTES AND TECHNIC OF ADMINISTRATION

Because of the rapid excretion of penicillin (see a later paragraph) frequent injections are necessary unless the material is given by continuous infusion. The standard procedure is to inject one eighth of the twenty-four hour dose deep into the gluteal (or other) muscle or into a vein every three hours day and night. Following an intravenous injection the blood level of penicillin promptly rises to a considerable height. According to the observations of Rammelkamp and Keefer [4] values of 1 or 2 Florey units per cubic centimeter of serum may be attained with a dose of 20,000 units, but there is a prompt drop so that within an hour or two barely measurable amounts remain. Following an intramuscular injection the blood level is lower but more sustained. At any rate it is to be noted that with intermittent injections one obtains peaks followed promptly by periods during which little if any penicillin remains in the blood stream. Whether such a state of affairs is less or more effective than a continuous, even if submaximal, blood level is not yet known. Both methods have produced satisfactory results, as will be pointed out.

One great disadvantage of injecting penicillin at three hour intervals is the inconvenience of this procedure. Either the doctor or a trained nurse must be available all night; if several patients are simultaneously under treatment it requires nearly the full time of some one to make the injections. Intramuscular injections are usually given with penicillin in high concentration—as much as 5,000 units per cubic centimeter of water or saline solution; they are not uncommonly followed by some local discomfort, and the patient also may be disturbed by the frequent needling. One man who was treated at various times by continuous subcutaneous and intravenous infusion and later by intermittent intramuscular injections objected to the latter procedure as the most annoying. Intermittent intravenous injections are usually arranged so that the dose (about 15,000 units) is given in 10 to 20 cc. of isotonic solution of sodium chloride.

Continuous Subcutaneous Infusion.—The subcutaneous administration of penicillin by the drip method has been extensively used in the Stanford clinic. The dose for a twenty-four hour period is prepared and given as follows:

Sterile 1,000 cc. bottles of isotonic solution of sodium chloride or 5 per cent dextrose are procured. We have used commercial products which are stated to be pyrogen free. If the dose for the day is 200,000 units or less, the total amount is dissolved in 1,000 cc. of fluid. We use saline solution unless there is a contraindication to the introduction of salt. The usual apparatus for subcutaneous clysis is set up with a dropper inserted so that the exact rate of flow of the solution can be checked. The system is filled with about 200 cc. of the penicillin solution, and the needle is introduced into the loose subcutaneous tissue of the thigh. The speed of flow is then so regulated that it will take twenty-four hours for the entire quantity of 1 or 2 liters to run in. If the total is 1,000 cc., the solution runs at approximately 10 drops per minute. Because of possible deterioration at room temperature, the bulk of the solution is kept in the refrigerator and from time to time amounts of 100 to 200 cc. are added to the solution in the infusion bottle. The attendants must watch the site of injection carefully to see that there is no large local collection of unabsorbed fluid; if collection occurs, the needle should be reinserted at another point. In our experience this rarely needs to be done oftener than every six to twelve or even twenty-four hours. A good deal of supervision of the whole procedure is necessary. The flow usually does not remain entirely constant over long periods; the number of drops per minute must be increased or decreased from time to time so as to consume as nearly as possible exactly twenty-four hours in introducing the entire dose. Before the subcutaneous drip is started we often give a single priming dose of 15,000 to 20,000 units into a vein to raise the blood level quickly.

Advantages and Objections to the Foregoing Method.—In some of the early cases especially the site of injection became extremely painful even when the flow was well regulated. As the solutions of penicillin are isotonic and neutral in reaction, the explanation was at first not clear. It is possible that some of the early lots of penicillin, which were highly colored (brownish yellow to yellow), contained irritating substances; there has been much less trouble with recent, more highly purified products which in the dilutions used have only a faint yellowish tinge. Small amounts of procaine hydrochloride added to the penicillin infusion also seem to have been effective in preventing local pain. In certain of the early cases there were sharp febrile reactions, the temperature rising to 39 to 40 C. (102.2 to 104.0 F.). Some of these reactions may have been due to pyrogenic saline solution or to stale infusion sets but more likely were caused also by

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Dr. Chester S. Keefer, chairman of the Committee on Therapeutic and Other Agents gave assistance and advice.

This paper, in a symposium on "Antibiotic Agents," is published under the auspices of the Section on Experimental Medicine and Therapeutics.

1. Keefer, C. S., and others: Penicillin in the Treatment of Infections, J. A. M. A. **122**: 1217 (Aug. 28) 1943.

2. Abraham, E. P.; Chain, E., and Holiday, E. R.: Purification and Some Physical and Clinical Properties of Penicillin, Brit. J. Exper. Path. **23**: 103 (June) 1942.

3. Abraham, E. P., and others: Further Observations on Penicillin, Lancet **2**: 177 (Aug. 16) 1941.

4. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.

impurities associated with the penicillin. Such reactions too are less frequent with recent lots.

The obvious advantages of continuous subcutaneous clysis are (1) the procedure once started is simple and can be watched by a nurse or other attendant, (2) it involves but little discomfort to the patient as frequent needling is avoided, and (3) the extremities do not have to be immobilized when the patient sleeps as they do with continuous intravenous drip. We have treated patients for several days to a week by the continuous subcutaneous drip without any technical difficulty.

The question of greatest importance is whether penicillin is as effective when given subcutaneously as when introduced into the blood stream. Rammelkamp and Keefer [4] report the prompt recovery in the urine of about two thirds of intravenously injected penicillin. Observations in our clinic by Rantz and Kirby [5] indicate that under certain conditions the excretion of penicillin after intravenous injection approaches 100 per cent. It is possible that penicillin given subcutaneously may stay in the tissues longer and perhaps exercise some effect even though the blood levels are lower than after intravenous injections. This part of the subject is still under investigation, and much more work needs to be done. At any rate the values of penicillin per cubic centimeter of plasma [6] when 100,000 units is given in twenty-four hours are approximately 0.05 unit (subcutaneous clysis) and 0.10 unit (intravenous drip). It is our feeling at present that while the subcutaneous route is adequate in gonococcic and perhaps some other infections it should not be used in staphylococcic sepsis, in which relatively high blood levels are probably necessary in order to extirpate the infection. If the continuous intravenous drip cannot be given, intermittent intramuscular injections, perhaps combined with subcutaneous clysis, would be the best alternative.

Continuous Intravenous Injection.—The intravenous route for administering penicillin by the drip method seems to us the route of choice in severe septic infections. The preparation of the material and that of the apparatus are the same as for subcutaneous infusion except that an intravenous needle is used. With cooperative patients one can use the small veins of the hand or the foot; for the most part the only immobilization of the needle necessary is that obtained with a bit of adhesive tape and a light bandage; at night a splint is used. With restless, delirious or uncooperative subjects a partial cast is necessary.

Our earlier patients treated by intravenous drip often had violent febrile reactions. Bouts of this sort have been much less frequent with the recent lots of penicillin. In some of the early patients too thrombosis of veins occurred. This is now largely avoided by (1) availability of less irritating penicillin, (2) giving the material in no higher concentration than 100,000 units per liter and (3) not allowing the needle to stay more than twelve to twenty-four hours in the same vein. One patient became edematous after five days of intravenous therapy. It was calculated that he had received from 20 to 30 Gm. of sodium chloride daily; a change from saline to 5 per cent dextrose solution as a solvent for the sodium salt of penicillin was followed by disappearance of the swelling.

In 1 patient intrasternal drip was used. This method deserves further trial. We have employed a combination of methods in the same case, such as intravenous drip by day and subcutaneous infusion at night.

Penicillin is highly effective when injected into closed cavities in which the drug can be retained. In empyema, for example, the injection of 25,000 to 50,000 units may be followed by prompt sterilization, as in the following case:

Case 1.—A 7 year old child had pneumococcic pneumonia about seven weeks before her entry into Stanford University Hospital. She had been treated with a sulfonamide compound without recovery. Empyema was diagnosed at that time but nothing further was done. On admission the child was prostrated, with typical signs of fluid in the left thoracic cavity, high irregular fever, serious anemia and leukocytosis. Fluid removed from the chest showed a pure growth of the type 1 pneumococcus. Thoracotomy was done and a tube inserted, but no improvement took place and the child seemed to be failing rapidly. On the sixth hospital day 30,000 units of penicillin in 50 cc. of saline solution was injected through the drainage tube, which was then closed with a clamp. Within twelve hours she was clinically well; her temperature was normal and remained so, and all fluids subsequently obtained from the chest were sterile. Several more doses of penicillin were injected through the tube, but they were probably unnecessary.

We have had no experience with injecting penicillin into infected joint cavities or intraspinally in meningitis. The treatment will doubtless be highly effective in certain cases. On the other hand, instillation of penicillin in chronic osteomyelitic sinuses has so far in our hands been useless, possibly because the organisms are not reached, possibly because the drug drains out before it acts in effective concentration. Tiny catheters inserted to the very depths of a sinus and flushed at frequent intervals with solutions of penicillin did not solve this problem.

DOSAGE

The dosage of penicillin has been largely arbitrary, and minimum effective amounts for various infections remain to be worked out. As long as the material is so difficult to prepare, economy is of the utmost importance. The penicillin commission at first advised that approximately 15,000 units be injected every three hours or roughly 100,000 units daily. We have used from 50,000 to 400,000 units daily in different situations largely on an empirical basis. Extensive studies by Rantz and Kirby [5] of blood levels following varying doses of penicillin show that even after continuous intravenous infusion at the rate of 20,000 units per hour plasma levels of only 0.4 to 0.5 Florey unit are obtained. With injection at the average rate of 100,000 units per day the level is only about 0.1 unit. As penicillin may be effective in the test tube in dilutions of over 1 : 100,000,000 it is impossible as yet to say definitely whether blood levels above some critical value increase therapeutic efficiency. However, Rammelkamp and Keefer [7] found that with staphylococcic infection

5. Rantz, L. A., and Kirby, W. M. M.: To be published.

6. The concentrations of penicillin in the blood and the urine were determined by a modification of the method of Rammelkamp (Proc. Soc. Exper. Biol. & Med. **51**: 95, 1942) and by a method devised by one of us (Kirby).

7. Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for Hemolytic Streptococcus and Staphylococcus Aureus, J. Clin. Investigation **22**: 649 (Sept.) 1943.

a blood level of at least 0.15 unit per cubic centimeter is necessary to obtain maximum bactericidal effect. Our largest doses were given for serious staphylococcic infections, after previous experience had shown how difficult it is to extirpate the organisms, partly with the hope of quicker and more complete effect and partly with the idea that "drug fastness" of surviving germs would be less likely to occur. On the other hand, it seems clearly established that most patients with acute and subacute gonorrhea can be sterilized (of gonococci) and clinically cured in a period of one or two days by doses of from 50,000 to 200,000 units given by a number of routes.

In certain types of infections, as will be pointed out presently, it is extremely difficult to tell when the patient is cured. In staphylococcic sepsis, especially, bacteria may fail to grow in blood cultures, demonstrable lesions may heal, temperatures may decline or be normal and still within a few days after treatment is stopped blood cultures are again positive and lesions recur. This is especially true when bone is involved. In one case a particularly interesting phenomenon was observed. Blood cultures negative after treatment with penicillin was stopped became positive again after a few days even though the patient's temperature was practically normal. The staphylococci under these conditions grew out very slowly; the colonies were not visible until the seventh to tenth day, as if the organisms had been altered in some way, perhaps partially inhibited.

A final point in regard to dosage is whether it should vary with the age and the size of the patient. Here again there are no conclusive data but we are inclined to base the dosage mainly on the character and the severity of the infection.

TOXICITY

We have observed no toxic effects from penicillin. Thrombosis of veins and fever and local irritation caused by impurities, pyrogenic water or stale infusion sets have, as pointed out in an earlier paragraph, occurred at times but these do not seem to be essential effects of the drug. One is completely delivered from the sort of worry he has when using sulfonamide compounds or arsphenamines; there seems to be no injury of kidneys, liver, bone marrow or brain, and no cutaneous rashes have been seen in our cases with the exception of urticaria in 1 instance. Even such a large daily dose as 400,000 units is a minute fraction of the amount of penicillin which has been found to be toxic in animals.

RESULTS

Penicillin has been reported to be effective against infections with certain strains of the pneumococcus, the hemolytic streptococcus, the gonococcus, the meningococcus and the staphylococcus.[1] Some nonhemolytic streptococci seem to be little affected, and the result in Streptococcus viridans endocarditis has, like that with every other measure, been a failure. Unfortunately the colon-typhoid group seems definitely not affected. As to certain other organisms there have been conflicting reports; with regard to viruses and molds the full potentialities have not yet been explored. The material is said to be useless in malaria. In primary syphilis treponemes rapidly (in six to fifteen hours) disappear from surface lesions, which heal in ten days to two weeks; the ultimate results are of course not yet known.

Our experience has included infections with the gonococcus, the streptococcus, the pneumococcus, the staphylococcus and Treponema pallidum and can be best presented by illustrative case reports.

Gonococcic Infections.—It is now well established that penicillin is extremely effective in gonococcic infections.[8] It is especially useful in those in which the organisms have become resistant to the action of sulfonamide compounds. The following 2 cases show that even after infection has been present for months it can still be rapidly controlled:

Case 2.—A 25 year old woman entered the hospital with a history of gonorrhea of two months' duration. For three weeks there had been excessive vaginal discharge, severe pain in the lower right quadrant of the abdomen and fever. Intensive treatment with sulfadiazine, hot douches and diathermy had failed to alleviate the condition. There was pronounced tenderness in the right lower quadrant and on pelvic examination there was tenderness in both adnexal regions. There was moderate leukocytosis, and many gonococci were grown in cultures of material from the cervix. The diagnosis was subacute gonococcic pelvic inflammatory disease, and 180,000 units of penicillin was given by subcutaneous infusion over a period of seventy-two hours. Within twenty-four hours after the start of treatment she felt well, the abdominal pain had practically disappeared, the temperature, which had been 100 F., fell to normal and cultures of material from the cervix were negative. On discharge from the hospital one week later she seemed entirely well.

The case illustrates very rapid cure in a woman of subacute, well intrenched gonococcic infection which had been resistant to all other modes of therapy. It is to be noted that the subcutaneous route was effective.

Case 3.—A man aged 34 had been treated two months previously with full doses of sulfathiazole for acute anterior urethritis with an apparently good result. When seen by us there was only a trace of thin discharge with some tenderness of the epididymis. However, cultures of both urine and prostatic secretion yielded many colonies of gonococci. He was treated with 100,000 units of penicillin by continuous intravenous drip over a period of twenty-four hours, following which on two occasions cultures of urine and prostatic fluid yielded no gonococci. The clinical residue of symptoms promptly disappeared. There was decided improvement of his general well being.

A subacute gonococcic urethritis, prostatitis and epididymitis of two months' standing, resistant to treatment with sulfonamide compounds, was clinically and bacteriologically cured in twenty-four hours.

Another patient with fresh gonococcic urethritis and subacute arthritis of the wrist was promptly cured of his urethritis, but the arthritis persisted. The joint trouble had not been proved, however, to be gonococcic.

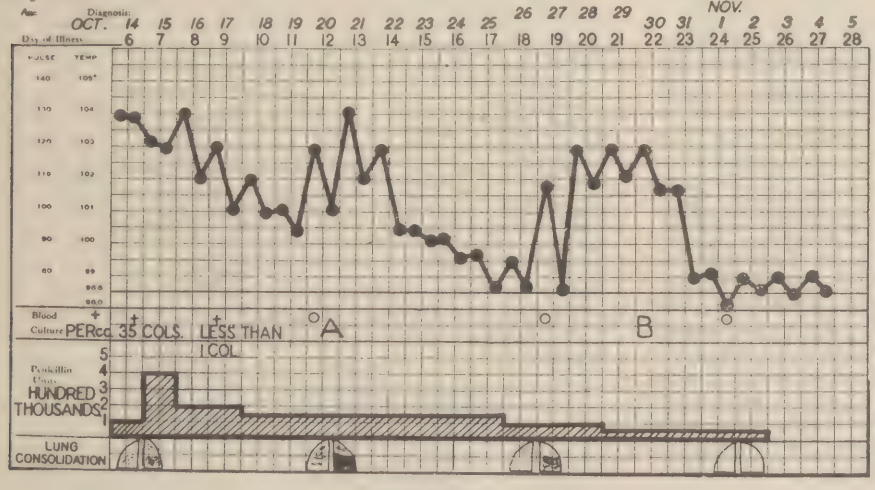
In summary, then, some of the most reliable and prompt results of penicillin therapy are obtained in patients with fresh or subacute gonococcic infection. In many patients, including those in whom the gonococci are resistant to treatment with sulfonamide compounds, a total quantity of 60,000 to 100,000 units given in divided doses intramuscularly or by continuous subcutaneous or intravenous drip is effective. Needless to say, a careful clinical and bacteriologic

8. Mahoney, J. F.; Ferguson, C.; Buchholtz, M., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide Resistant Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **27**: 525 (Sept.) 1943.

follow-up should be conducted on these patients preferably for several months.

Streptococcic Infections.—The wide field of streptococcic infections is only beginning to be explored. Hemolytic streptococci are perhaps less readily controlled than gonococci but are more easily controlled than staphylococci. This is a general statement subject to many exceptions depending on the type and the extent of the lesions. S. viridans, especially in subacute bacterial endocarditis, is little if at all affected. The following case shows, however, that penicillin may exert a favorable influence on a severe infection with nonhemolytic streptococci:

CASE 4.—A man 50 years old was hospitalized from June 14 to July 19, 1943 for treatment of a subphrenic abscess on the right side, which had probably developed on the basis of an undiagnosed rupture of the appendix. Following surgical drainage and administration of sulfadiazine he made what was believed to be an uneventful recovery. On August 20 he returned complaining that he had been ill with chills and fever for the three previous days. There were high "septic" fever and definite leukocytosis, but a blood culture was sterile. The abdomen was explored and at least three abscesses were found in the left lobe of the liver from which pus was recovered that yielded a pure growth of an anaerobic nonhemolytic streptococcus. The site of the old subdiaphragmatic abscess was explored and was found to contain a little pus. Both incisions were drained, and sulfadiazine was given, but the patient failed to improve. He was desperately ill, and since the organisms isolated from the hepatic abscesses were shown in vitro to be very sensitive to penicillin, administration of this material was begun on the eighth hospital day. He received from 50,000 to 200,000 units daily, mostly by subcutaneous and intravenous routes, for seven days—a total of 600,000 units of penicillin being given. During treatment he seemed much improved generally but continued to have an irregular fever, the temperature rising to 102 to 104 F. daily. Soon after the penicillin therapy was discontinued, however, his temperature became lower, and since Escherichia coli was now demonstrated in the drainage from his incisions, sulfadiazine was again administered in the usual dosage. He improved steadily; his temperature became normal, and his incisions healed. He left the hospital on August 22, thirty-three days after the start of penicillin therapy. On October 15 he wrote enthusiastically that he was entirely well.



Course in case 5.

It is extremely difficult to evaluate the effect of penicillin in this case. It certainly did not produce an immediate cure, but it seemed to "turn the tide" in a patient who all observers felt was moribund.

notes

Staphylococcic Infections.—Staphylococcic infections, although undoubtedly responsive to penicillin, present an extremely difficult problem. In severe infections several weeks of intensive treatment may be necessary before a cure is achieved. Even then what appears to be a cure may be spurious, and organisms left dormant may revive and reinitiate active infection. The explanation of this peculiarity of staphylococci in relation to penicillin may be related to test tube experiments which have shown that even large doses of the drug fail to kill quite all the organisms if the inoculum is heavy. The theoretical aspects of this interesting fact have been discussed by Rammelkamp and Keefer[7] and others but cannot be gone into further here. It is also possible that surviving organisms may become penicillin resistant.

At any rate severe staphylococcic infections seem definitely

to fall into two groups as regards response to penicillin. If the lesions are fresh and not walled off by heavy sinus tracts, or if they are accessible to thorough surgical evacuation, cures may be achieved even in desperately ill patients with multiple foci and bacteremia. If, on the other hand, chronic bone lesions, especially deep sinuses with thick walls and sluggish drainage, are present and cannot be surgically extirpated, it is much more difficult to accomplish anything.

Doses for staphylococcic infections must be considerably higher than those which are effective, for example, in gonorrhea. It is our feeling at present that for severe staphylococcic disease in an adult 300,000 to 400,000 units per day should be given until things are definitely on the mend and that a dosage of 150,000 to 200,000 units a day thereafter should be continued until the patient is well. Such doses are necessary to reach or surpass the blood level of 0.15 Florey unit per cubic centimeter of blood which Rammelkamp and Keefer [7] found to be necessary to achieve maximal killing of staphylococci in vitro. The intravenous rather than the subcutaneous route should be used for continuous infusion. If there is any contraindication to the introduction of large amounts of fluid, intramuscular injections of a concentrated solution of penicillin can be given. These principles are illustrated in the following cases.

Case 5.—The patient was a 31 year old laborer who appeared moribund, and the history was obtained indirectly. Five days previously a carbuncle developed in the left scapular region. He rapidly became gravely ill with chills, fever, delirium and stupor. Two days later the carbuncle was incised, and he was given full doses of sulfathiazole. The blood culture was said to be positive. He did not respond and was sent into Stanford University Hospital. He was a red faced, sweating, dehydrated man, apparently dying. A huge fiery carbuncle with induration 20 cm. in diameter had been incised, and there was drainage of thin pus from which Staph. aureus was grown. There were scars of small furuncles on the right hand and arm. The respirations varied from 50 to 80 per minute, and there was dulness at the base of the right lung with many rales, and scattered patches of rales were heard through both lungs. The leukocyte count was 18,000, and the blood on culture yielded 35 colonies of Staph. aureus (coagulose positive) per cubic centimeter. The diagnosis was staphylococcic sepsis with bacteremia, carbuncle and extensive staphylococcic pneumonia (metastatic).

Penicillin was given by intravenous drip at the rate of 400,000 units for the first day, later decreasing (see chart) to 150,000 units and finally to 50,000 to 60,000 units daily. A total of 2,560,000 units was given over a period of twenty days. For the first nine days there was no notable improvement although the patient seemed a little less toxic. The carbuncle resolved steadily, but pneumonia continued and there were frank signs of solidification of the lower lobe of the right lung. On the ninth day there was amazing improvement; the temperature fell rapidly, the patient became bright and said he felt well, and the signs of disease in the lungs began to resolve. By the twelfth day the temperature was normal. From the fifteenth to the seventeenth day elevations up to 39.5 C. (103.1 F.) recurred, but the temperature dropped immediately when a fresh infusion set was used. By the twentieth day he seemed cured; the lungs were almost clear, the carbuncle was healed and the temperature was normal. The accompanying chart shows his course graphically.

This is the sort of staphylococcic infection, sulfathiazole resistant and almost invariably fatal, which may respond brilliantly to penicillin. Note that there were no old walled off lesions. Two other points are important: In spite of large doses of penicillin there was not much change for over a week; this is the rule in staphylococcic sepsis of this type, contrasting with the "overnight" cure of gonorrhea. Infusion sets should be changed frequently, as molds and other organisms may grow in penicillin and produce pyrogenic material.

Case 6.—A 15 year old boy entered the hospital for penicillin therapy because of chronic osteomyelitis. Lesions had been recurring for twenty-six months, involving the left ankle, knee and groin, the right ankle and thigh and the back. On entry there were three sinuses draining greenish pus from which Staph. aureus (coagulase positive) was grown. One sinus ran deep into the spine. All were associated with chronic destructive lesions in bone, as definitely shown in roentgenograms. There had been numerous surgical operations in the past. He was a chubby boy, slightly pale. Physical examination showed nothing remarkable except the scars and sinuses. There were slight elevations of temperature and slight anemia (hemoglobin content 72 per cent, Sahli). Between September 21 and November 1 he received 2,225,000 units of penicillin mostly by intravenous drip but at times by subcutaneous clysis. The daily dose varied from 60,000 to 200,000 units. Between October 8 and 18 about 40,000 units in a solution of 100 units per cubic centimeter of saline solution was injected deep into the anterior sinus (5 cc. every three hours).

The results of all this treatment were disappointing. Drainage was not lessened, sinuses did not close, and cultures remained positive.

In this case low grade staphylococcic sepsis and multiple osteomyelitic sinuses with thick walls failed to respond to penicillin therapy. It is possible that larger doses over a longer period would accomplish more, and further intensive therapy is planned in connection with an operation for removal of a sequestrum. At best, however, the problem is much more difficult than in the type presented in case 5. In another case an acute staphylococcic abscess of an arm, which was opened and drained, cleared up, while a chronic sinusitis of the leg was not affected. Undoubtedly surgical cleaning out of necrotic bone helps greatly to render the organisms accessible to penicillin. This is illustrated further in the following case:

Case 7.—A woman aged 32 had had chronic sinusitis involving the frontal and maxillary sinuses for at least four years. Four weeks before entry the right antrum was drained, and one week later swelling and tenderness of the overlying tissues developed. Seven days' administration of sulfonamide compounds did not help. On examination the right side of the face was swollen so that the eye was nearly closed and the nasolabial fold obliterated. The skin was red and shiny and very tender on pressure. There was a draining sinus above the alveolar process over the canine tooth on the right. Thick yellow pus came from this area. The alveolar process seemed to be loose. The diagnosis was osteomyelitis of the right maxilla. Culture showed a variety of bacteria including a heavy growth of Staph. aureus (coagulase positive). There were swings of the temperature up to 39.5 C. (103.1 F.).

Otolaryngologists as consultants pointed out that in their experience bone infections of this sort always progress to a fatal issue. Between September 25 and October 31 the patient received 2,690,000 units of penicillin by intravenous and subcutaneous drip in doses of 45,000 to 200,000 units daily. Two operations were performed for the removal of necrotic pieces of bone. Her disease ran a stormy course with several exacerbations, but by November 1 the temperature was normal. It has now remained normal for twelve days, she feels well, all drains are removed and the sinuses are closing.

The importance of a combination of surgical drainage and removal of dead bone with the continuous

injection of penicillin is to be emphasized. In spite of the treatment with penicillin this patient continued to have exacerbations until such surgical measures had been instituted. On the other hand, it is said that surgical treatment alone never arrests the relentless progress of osteomyelitis in patients with involvement of bones of the face of this type.

SYPHILIS

The rapid disappearance of Treponema pallidum from surface lesions and the resolution of early lesions under penicillin therapy have recently been reported.[9] These observations we have confirmed without exception in a series of 7 cases of early (seronegative and seropositive) syphilis. A typical example is as follows:

CASE 8.—A young Negro noticed a penile lesion fourteen days and swollen glands in the groins two days before entering the hospital. He had a typical chancre, 1.2 cm. in diameter, and large inguinal lymph nodes. The Wassermann reaction was negative, but huge numbers of typical, actively motile treponemes were seen in dark field preparations from the primary lesion. He received 200,000 units of penicillin by intravenous drip daily for five days—a total of 1,000,000 units. Twelve hours after the start of treatment only a rare treponeme was seen; two hours later none were found. There was rapid involution of the chancre and nodes over a period of ten days.

In other cases condylomas have become free of treponemes in approximately twelve to twenty hours. In 1 patient with an extensive but pale roseola there was a violent flare-up of all the lesions within a few hours after the infusion of penicillin was started, a phenomenon probably analogous to the Herxheimer reaction. The lesions became bright red and palpable. This was followed by rapid clearing.

It seems clear then that immediate results comparable to those obtained with full doses of arsphenamine can be achieved. However, this by no means indicates that treponemes have been completely destroyed throughout the body and that recurrences, perhaps resembling those seen in patients inadequately treated with arsphenamine, will not take place later. The most careful observation and control of penicillin treated patients are necessary for a long period before any conclusion can be drawn as to the ultimate effect. Quantitative serologic tests at frequent intervals, thorough physical examination and later examination of the spinal fluid must all be done over a period of years to determine the final results. Dosage also has so far been purely tentative. It is clear, then, promising as these immediate results in syphilis seem to be, that the use of penicillin should still be restricted to the most careful experimental study of selected cases. The whole matter of penicillin treatment for syphilis is now being supervised by committees of the National Research Council and by the Committee on Medical Research of the Office of Scientific Research and Development.

COMMENT AND SUMMARY

These experiences with penicillin therapy serve largely to emphasize the unsolved problems. The best route of administration and the optimum dosage of penicillin for various infections are as yet unsettled. Formulation of a sort is however possible. It is established that gonococcic infections can usually be cured in a day or so by a total dose of 60,000 to 100,000 units given by intravenous drip, by subcutaneous clysis or by divided intramuscular injection. Staphylococcic infections, on the other hand, are much more stubborn and even in favorable cases days or weeks elapse before cure is effected. It is our impression that a much higher dose of penicillin (200,000 to 400,000 units per day) should be given in the early stages of severe staphylococcic infection and that the dose should never be under 120,000 units for an adult of average size. Continuous intravenous drip has been successful in our hands in staphylococcic infections whereas subcutaneous clysis is likely to be ineffective because of the lower blood levels obtained by this method, although the last word on the subject is not yet said. Intermittent intramuscular injections seem to us a less satisfactory method of treating severe staphylococcic sepsis, but our experience is mainly with intravenous administration. In any event, in every case the dose of penicillin and the route of administration should be carefully planned each day. One is guided by the clinical situation, the bacteriologic findings and the measurements of the blood level of penicillin. These principles apply to any infection for which penicillin is used.

2361 Clay Street.

9. Mahoney, J. F.: Paper read before the American Public Health Association.

PENICILLIN THERAPY OF SURGICAL INFECTIONS IN THE U. S. ARMY

8

A REPORT

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On April 1, 1943 the Office of the Surgeon General, U. S. Army, sponsored a pilot unit for penicillin therapy at the Bushnell General Hospital at Brigham City, Utah. A second unit was established at Halloran General Hospital, Staten Island, New York, on June 3, 1943. Both of these units have functioned as "schools" in penicillin therapy, and selected medical officers have been trained for one month periods to use penicillin in accordance with an overall program seeking definition of the effectiveness of the drug in surgical infections. It is the purpose of this report to summarize the experience of these trained observers as reported from several general hospitals within the Zone of the Interior.

During this period of evaluation of a new drug it has seemed wise to concentrate experience as far as possible. Each general hospital has set aside a ward unit for penicillin therapy under direction of a trained medical officer and the chief of the surgical service. With few exceptions these wards have provided single rooms or cubicles for each patient. Surgical dressings have been done under operating room conditions. Patients and attendants have been masked, dressers have been scrubbed, gowned and gloved, and individual sterile dressing packets of instruments have been used. Every effort has been taken to prevent cross infection and secondary contamination of wounds.

At one of the units (Halloran General Hospital) special bacteriologic and chemical laboratory facilities have been set up. At other hospitals an especial liaison has been established with the routine laboratories to allow for preferential treatment of problems in the penicillin ward.

The program as outlined has been concerned with surgical infections and has not included the treatment of sulfonamide resistant gonorrhea. The accumulated data will be reviewed in the following order:

I. Penicillin: Methods of administration, dosage and reactions.

II. Experience in the treatment of acute pyogenic infections.

III. Experience in the treatment of chronically septic compound fractures with observations on the bacteriology of war wounds and the anemia of chronic sepsis.

I. PENICILLIN

Methods of Administration.—Both the intravenous and the intramuscular routes have been used extensively for intermittent injections. In unskilled hands the incidence of thromboses after intravenous injection is sufficiently great to make the intramuscular route preferable. The deltoid and gluteus muscles have been used most frequently. The intramuscular route has proved practical, and no contraindication to its continued use has been observed.

The constant intravenous method of treatment has been preferred for immediately life endangering infections. Penicillin has been dissolved in 5 per cent dextrose or isotonic solution of sodium chloride for constant drip administration, or injections of concentrated solutions have been made at frequent intervals directly into the tubing or into an adapter valve in the tubing.

Local application of the powdered sodium salt of penicillin is too irritating for general use.[1] Concentrations up to 5,000 units per cubic centimeter have been used occasionally, but the usual preparation has contained 250 units per cubic centimeter. The antibacterial activity of such solutions has been demonstrated in exudates for twenty-four hours after a single local application. More frequent applications may be necessary under particular circumstances, but the single daily application is usually adequate to keep the wound clean and free from pyogenic cocci. Penicillin has been injected through tubes and spigots, has been incorporated into ointments and has been applied as a wet dressing.[2] Both calcium and sodium salts have been used. The nature of the wound is the chief factor in the selection of the method or vehicle for local application.

The inability of investigators [3] to demonstrate penicillin in spinal fluid after intravenous or intramuscular injection has led to a recommendation of intrathecal injection for patients with meningitis. Ventricular fluid has been shown to possess an antibacterial effect following an injection of penicillin into the lumbar space. Spurling [4] has expressed a preference for the injection of penicillin into the lateral ventricles through a burr hole as more likely to insure better diffusion of the drug from above downward than vice versa. In any event, it is important to make certain that there is no intrathecal block in a case treated through a single site of injection. Enough experience has been accumulated to state that lumbar, cisternal and ventricular routes are all practical.

Reactions to Penicillin.—Increasing experience leads to the conviction that certain untoward reactions are peculiar to particular batches of the drug and are attributable to toxic impurities rather than to the active penicillin fraction. Such impurities constitute 80 to 90 per cent of the final product and may vary from batch to batch in the hands of a single producer. It is our impression that deeply colored penicillin which foams during preparation or contains a nonfiltrable residue is most apt to give reactions. The yellow pigment is not the active agent.[5]

The reactions associated with particular batches of penicillin and thought to be due to impurities are:

1. Chills with or without fever after intravenous injection.
2. Eosinophilia of 20 to 30 per cent.
3. Burning pain at the site of intramuscular injection.
4. Headache.
5. Faintness and flushing of the face.
6. Unpleasant taste after parenteral injection.
7. Tingling in testes.
8. Muscle cramps.
9. Femoral phlebothrombosis.

Most of these reactions were encountered during the developmental period of penicillin therapy and could be prevented by Seitz filtration of the solution before injection. Such precautions are no longer generally necessary, and the various commercial products are satisfactory for use as issued. It should be noted, however, that about half the patients will experience a transient burning discomfort at the site of intramuscular injection during the first forty-eight hours of treatment but not thereafter.

There is an extremely low incidence of untoward reactions attributable to products of penicillin available at present. This product still contains many impuri-

The work reported herein was done under the auspices of the Office of the Surgeon General, U. S. Army, and with the cooperation of the Committee of Medical Research of the Office of Scientific Research and Development.

The clinical work has been directed by Lieut. F. W. Cooper, M. C., Ashford General Hospital; Lieut. Col. R. B. Grant Jr., M. C., Brooke General Hospital; Lieut. Col. H. G. Hollenberg, M. C., Lieut Col. F. B. Queen, M. C., Major J. E. L. Keyes, M. C., Major J. M. Walker, M. C., Capt. T. F. Barrett, M. C., Capt. A. J. Ingram, M. C., and Capt. W. J. Morginson, M. C., Bushnell General Hospital; Lieut. Col. V. S. Johnson, M. C., Major G. K. Carpenter, M. C., and Capt. K. F. Mech, M. C., Halloran General Hospital; Lieut. W. I. Glass, M. C., Kennedy General Hospital; Capt. A. L. Evans, M. C., Lawson General Hospital; Major C. V. Ervin, M. C., Letterman General Hospital; Major G. F. Wollgast, M. C., McCloskey General Hospital; Lieut. J. M. Ferrer Jr., M. C., Percy Jones General Hospital; Capt. W. H. McKean, M. C., Valley Forge General Hospital, and Capt. J. E. Hamilton, M. C., Walter Reed General Hospital.

The laboratory studies have been under the supervision of Lieut. R. Rustigian, Sn. C., and Barbara J. Silverman for bacteriology and G. Margaret Rourke, B.A., Eleanor G. Fogerty, B.A., and Jane LeFetra, B.S., for chemistry.

Col. Ralph G. DeVoe, M. C., U. S. Army, commanding officer, Halloran General Hospital, and Col. Robert M. Hardaway, M. C., U. S. Army, commanding officer, Bushnell General Hospital, gave invaluable advice and cooperation in the establishment and maintenance of the penicillin units.

Valuable assistance was given by Drs. A. N. Richards, A. Baird Hastings, A. R. Dochez, Chester Keefer and Major John D. Stewart, M. C., A. U. S.

1. Clark, A. M.; Colebrook, L.; Gibson, T., and Thompson, M. L.: Penicillin and Propamidine in Burns: Elimination of Hemolytic Streptococci and Staphylococci, Lancet **1**: 605 (May 15) 1943.
2. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**: 387 (March 27) 1943.

ties in addition to penicillin, so that it cannot be concluded that even these reactions are due only to penicillin. The most that can be said are that the following reactions have not been limited to particular batches of the drug:

1. Urticaria:
   (*a*) Without fever.
   (*b*) With fever to 101 F.
   (*c*) With fever to 103 F. and abdominal cramps.
2. Fever in the first five days of therapy.
3. Transient azotemia.
4. Thrombophlebitis at the site of constant intravenous injection.

Urticaria.—The commonest single complication is probably urticaria and occurred in 12, or 5.7 per cent, of 209 cases. It has occurred during every week of treatment, as early as the first day and as late as the fourth week. It has been reported once as a complication of local therapy alone. The lesions usually develop during treatment but may occur as late as nine days after treatment has been stopped. The wheals are widely distributed over the body, the face and eyelids become swollen, and there may be swelling of the fingers with joint pains in the hands. The process continues for three to five days and is usually benefited by epinephrine or ephedrine. The course is independent of continuance or cessation of treatment. Subsequent courses of penicillin therapy in patients with a history of urticaria during the first treatment period have been uneventful and not associated with recurrent urticaria.

The complications associated with urticaria are fever and abdominal cramps. The fever is present only when the urticaria is severe and does not usually exceed 101 F. Two patients receiving large doses of penicillin (400,000 and 600,000 units daily respectively) subsequently developed urticaria, fever to 103 F. and abdominal cramps with frequent formed stools. In two other patients an unexplained fever of 103 F. without urticaria has been noted on the eighteenth and twenty-seventh days respectively. The first of these patients had no other symptoms, but the second showed dermatographia, lacrimation, conjunctival injection and sneezing. These symptoms have suggested an analogy to serum sickness, but eosinophilia has not been definite. Tests for cutaneous and ophthalmic sensitivity during and after the reactive phase have been negative. Precipitins for penicillin have been absent in the serum of patients tested during the phase of urticaria. Heterophil agglutinins have been irregularly demonstrated by means of a system adjusted for maximal sensitivity, but such agglutinins have not been significantly and constantly increased.[6] However, chemical assays of penicillin have revealed only trace amounts of nitrogen, and the active drug is not a protein.[7] For practical purposes of clinical management the urticarial reaction may be considered an atypical sensitization phenomenon. It is atypical in the sense that the period of sensitivity is remarkably transient. Therapy may usually be continued through the period of urticaria, and subsequent courses of treatment reveal no evidence of persistent sensitivity.

Fever Without Urticaria.—In a few patients fever without urticaria has been noted during the first three to five days of treatment. Such fever is most apparent in patients previously afebrile, although it may also occur and cause some concern in patients with febrile infections. In general the temperature chart reflects clinical progress less dramatically than one might expect on the basis of experience with sulfonamides. There is no evidence that penicillin is antipyretic per se.

Transient Azotemia.—This has been reported during the course of treatment by the Floreys.[2] In some of their cases the blood urea nitrogen was moderately elevated during therapy but returned to normal after penicillin was stopped. Albuminuria was not noted. In the present series the nonprotein nitrogen content of the plasma has been followed. Transient elevations of 5 to 10 mg per hundred cubic centimeters have been recorded, but the total concentration has rarely exceeded 35 mg. per hundred cubic centimeters, the highest recorded value being 48 mg. per hundred cubic centimeters.[8] Hyaline casts have been noted occasionally in the urine, but albuminuria has been absent. No clinical significance has been attached to these lesser degrees of azotemia. The observations did suggest that penicillin might have some inhibitory effect on the enzyme urease. Experimentally, penicillin failed to inhibit the urease system of Proteus mirabilis.

Thrombophlebitis.—At the site of constant intravenous injection thrombophlebitis occurs frequently. The phlebitis is noticeable during the second day of injection and may lead to chills and fever if therapy is continued through the same vein. The complication may be avoided by the use of dilute solutions of penicillin and a daily change of the position of the needle. Active phlebitis does not occur at the site of intermittent intravenous injections, and the incidence of thromboses reflects the skill with which venipuncture has been performed. As many as 500 intravenous injections have been given to 1 patient without thrombosis of a single vein.[9] The hazard of pulmonary infarction as a consequence of thrombophlebitis in the lower extremity has led to the recommendation that all intravenous injections be given in arm veins.

Dosage of Penicillin.—The greatest difficulty attends precise definition of therapeutically effective dosage for penicillin. The limited supply of the drug has encouraged determination of the minimally adequate rather than the maximally tolerated dose, and there is a definite trend to higher dosage as more liberal quantities of the drug become available. Bioassays of penicillin activity have given fairly close agreement,

3. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342 (March) 1943; The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.
4. Spurling, Glenn, Lieut. Col., M. C., A. U. S.: Personal communication to the author.
5. Reid, R. D.: Some Properties of a Bacterial Inhibiting Substance Produced by a Mold: J. Bact. **29**: 215 (Feb.) 1935.
6. Serums from patients under treatment examined by Dr. W. H. Goebel, Rockefeller Institute, New York City, and Dr. C. A. Stuart, Brown University, Providence, R. I.
7. Abraham, E. P., and Chain, E.: Purification and Some Physical and Chemical Properties of Penicillin, with a Note on the Spectrographic Examination of Penicillin Preparations by E. R. Holiday, Brit. J. Exper. Path. **23**: 103 (June) 1942. Meyer, K.; Chaffee, E.; Hobby, G. L.; Dawson, M. H.; Schwenk, E., and Fleischer, G.: On Penicillin, Science **96**: 20 (July 3) 1942.

but it is possible to have variations of 25 per cent.[10] There is considerable variation in the stability of prepared solutions, and in certain instances it would appear that such changes were responsible for inadequate therapy. In addition, the susceptibility of bacteria to penicillin is variable not only from group to group but from strain to strain. To date it has been necessary to maintain laboratory controls of the potency of penicillin and bacterial susceptibility to insure uniformly successful results.

In general, the following suggestions in regard to dosage are valid:

Streptococcic Infections.—The group of streptococci includes resistant and susceptible species. Resistant forms have been encountered most commonly in the viridans group and the thermophilic (capable of growth at 45 C.) group of nonhemolytic streptococci (faecalis type). The susceptible species include most of the beta hemolytic, mesophilic nonhemolytic and some alpha hemolytic, or viridans, streptococci. Sensitive strains are usually extremely susceptible to penicillin. Adequate therapy for susceptible infections has been provided by 90,000 units of penicillin daily given as 15,000 units every four hours intramuscularly.

Staphylococcic Infections.—As a group the staphylococci require two to four times as much penicillin for inhibition as do susceptible strains of streptococci or pneumococci, but some strains of staphylococci are extremely sensitive. A recognized complication of therapy is the tendency of bacteria, particularly staphylococci, to become resistant, or "fast," to penicillin. Inadequate dosage tends to develop resistant strains. In our experience penicillin fastness has usually developed within the first week of treatment if it is to occur. Resistant strains have been responsible for persistence or recurrence of infection during treatment and for relapses after weeks of apparent cure. Occasional cases will progress to satisfactory healing in spite of the development of penicillin fastness by the infecting strain of staphylococcus. It has been shown that strains made resistant by in vitro passage in the laboratory develop degraded metabolic characteristics and attenuated virulence.[11] The coagulase activity and mannite fermentation of the resistant strains in this series have not been altered, and loss of virulence has not been apparent clinically. On the other hand, incomplete therapy does not lead necessarily to loss of sensitivity. A sensitive strain was recovered from a bone abscess of the femur two months after conclusion of treatment with 10,000,000 units of penicillin for a fulminating hematogenous osteomyelitis.

In summary, the hazard of penicillin fastness dictates intensive and effective initial dosage for all infections. It is particularly necessary to use large initial dosage for staphylococcic infections. For bacteremic infections the constant intravenous treatment is recommended with an initial dose of 25,000 units and 5,000 to 7,500 units every half hour thereafter for a total of 240,000 to 360.000 units daily. As much as 600,000 units daily has been required for such infections. As progress warrants, or as an alternative method for maintenance, a dosage of 25,000 units every three hours has provided 200,000 units daily. The latter dosage is routine for all nonbacteremic staphylococcic infections treated with the penicillin of present potency. It is known that this dosage will vary from one infection to another and from one particular product of penicillin to another.

Clostridial Infections.—The pathogenic clostridia have been found sensitive to penicillin,[12] but these are laboratory and animal observations. Dosage for human beings is uncertain because of lack of experience with the therapy of gas gangrene. No cases of gas gangrene have been reported in this series. The proteolytic clostridia recovered from war wounds require four to five times as much penicillin as do staphylococci, whereas organisms of the tetanus-tetanomorphum group are similar to streptococci in their sensitivity. These bacteria have been responsible for anaerobic cellulitis or putrefactive locally necrotizing infections and have been isolated in frequent association with Proteus bacilli of various types. Wound infection with these organisms in abundance is indicative of devitalized tissue or bone fragments. Systemic penicillin therapy in dosages of 200,000 units daily has controlled the associated anaerobic cellulitis but has not arrested suppuration as dramatically as in the cases of pyogenic coccic infection. Local therapy is almost a necessary supplement to systemic therapy; local therapy alone has not been as effective as combined therapy. Increasing the systemic dosage up to 400,000 units daily has not seemed to be more effective. Control of the anaerobic infection usually follows wound revision and sequestrectomy. The subsidence of inflammation is entirely clinical, for the clostridia persist in the wound throughout the period of healing in spite of intensive local therapy.

The problem of penicillin fastness among clostridial species has not been investigated. It is not uncommon to isolate clostridia for the first time from a wound by culture of a sequestrum removed at operation. As such cultures are made after a period of treatment has been given it is difficult to evaluate the observed relative sensitivity of the particular strain in terms of fastness.

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8. Patient of Lieut. J. M. Ferrer jr., M. C., Percy Jones General Hospital, Battle Creek, Mich.

9. Patient of Lieut. F. W. Cooper Jr., M. C., Ashford General Hospital, West Virginia.

10. Abraham, E. P.; Chain, E.; Fletcher, C. M. Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**: 177 (Aug. 16) 1941. Foster, J. W., and Woodruff, H. B.: Microbiological Aspects of Penicillin: I. Methods of Assay, J. Bact. **46**: 187 (Aug.) 1943.

11. McKee, C. M., and Houck, C. L.: Induced Penicillin Resistance in Pneumococcus Type III Culture, Federation Proc. **2**: 100 (March 16) 1943; Induced Resistance to Penicillin of Cultures of Staphylococci, Pneumococci, and Streptococci, Proc. Soc. Exper. Biol. & Med. **53**: 33 (May) 1943. Abraham, Chain, Fletcher, Gardner, Heatley, Jennings and Florey.[10]

12. Chain, E.; Florey, H. W.; Gardner, A. D.; Jennings, M. A.; Orr-Ewing, J., and Sanders, A. G.: Penicillin as a Chemotherapeutic Agent, Lancet **2**: 226 (Aug. 24) 1940. Dawson, M. H.; Hobby, G. L.; Meyer, K., and Chaffee, E.: Penicillin as a Chemotherapeutic Agent, J. Clin. Investigation **20**: 434 (July) 1941. Florey, H. W., and Jennings, M. A.: Some Biological Properties of Highly Purified Penicillin, Brit. J. Exper. Path. **23**: 120 (June) 1942. Gardner, A. D.: Morphological Effects of Penicillin on Bacteria, Nature, London **146**: 837 (Dec. 28) 1940. Hac, L. R., and Hubert, A. C.: Penicillin in Treatment of Experimental Clostridium Welchii Infection, Proc. Soc. Exper. Biol. & Med. **53**: 61 (May) 1943. Hobby, G. L.; Meyer, K., and Chaffee, E.: Activity of Penicillin in Vitro, ibid. **50**: 277 (June) 1942. McIntosh, J., and Selbie, F. R.: Zinc Peroxide, Proflavine and Penicillin in Experimental Cl. Welchii Infections, Lancet **2**: 750 (Dec. 26) 1942. Robinson, H. J.: Toxicity and Efficacy of Penicillin, J. Pharmacol. & Exper. Therap. **77**: 70 (Jan.) 1943.

II. PENICILLIN THERAPY OF ACUTE INFECTIONS

The results in the treatment of acute infections are in keeping with the findings of Keefer and his associates.[13] An analysis of reported cases is presented in table 1.

Bacteremias.—Six of 9 patients with staphylococcemia recovered. All the infections were severe. The three deaths included 2 instances of endocarditis and a secondary staphylococcic infection of an extensive atypical pneumonitis. It is of interest that in both instances of endocarditis the strains recovered before treatment were subsequently shown to be resistant to penicillin. In other words, penicillin fastness was inherent and not induced in the two endocarditis strains.

The 4 patients with hemolytic streptococcus bacteremia had failed to respond to sulfadiazine. The one death occurred during the first forty-eight hours of treatment from major intracranial thromboses secondary to frontal sinusitis.

The death recorded in consequence of a bacteremia due to pneumococci and nonhemolytic streptococci represents an instance of treatment of a moribund patient with pneumonia.

The mixed staphylococcus and nonhemolytic streptococcus bacteremia arose from an empyema. Rib resection was performed at the time penicillin therapy was started.

The recovery recorded for meningococcemia represents a complicated case. Sulfadiazine and meningococcic antiserum were given for acute meningitis and a retrobulbar abscess. The response was slow but progressive until the tenth day, at which time serum sickness developed with an exacerbation of the infection and the appearance of multiple metastatic abscesses. The meningitis did not recur, and the patient responded to intravenous penicillin therapy without intrathecal supplement.

A recovery is listed under the heading of salmonella bacteremia. The focus of infection was a large ischiorectal and retroperitoneal abscess containing beta hemolytic streptococci in quantity. It is likely that penicillin controlled the streptococcic component of the infection, whereas the clearance of the salmonella infection was merely coincidental.

A patient with Proteus bacillus bacteremia quite understandably showed no improvement and died. Penicillin is not effective against this organism.

Another patient succumbed during penicillin therapy for a mixed bacteremia due to Escherichia coli, Aerobacter aerogenes and nonhemolytic streptococci. A septic compound fracture of the pelvis and a pelvic abscess were associated with septic thrombophlebitis of the inferior cava and its tributaries.

13. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: A Report of 500 Cases, J. A. M. A. **122**: 1217 (Aug. 28) 1943.

TABLE 1.—*Analysis of Reported Cases*

	Number	Improved	Died	No Effect
Bacteremias				
Staphylococcus	9	6	3	0
Beta hemolytic streptococcus	4	3	1	0
Pneumococcus, nonhemolytic streptococcus	1	0	1	0
Staphylococcus, nonhemolytic streptococcus	1	1	0	0
Proteus bacillus	1	0	1	0
Meningococcus	1	1	0	0
Coli, aerogenes, nonhemolytic streptococcus	1	0	1	0
Salmonella	1	1	0	0
	19	12	7	0
Nonbacteremic staphylococcus infections				
Abscesses	12	11	0	1
Burns	2	1	1	0
Conjunctivitis	3	3	0	0
Empyema	2	2	0	0
Mastoiditis	3	1	0	2
Meningitis	2	2	0	0
Osteomyelitis	12	11	0	1
Osteomyelitis of skull	4	4	0	0
Parotitis	2	2	0	0
Skin and subcutaneous tissue	12	11	0	1
Urinary tract	4	4	0	0
Wound infections	21	17	0	4
	79	69	1	9
Nonbacteremic hemolytic streptococcus infections				
Cellulitis	5	5	0	0
Empyema	1	0	1	0
Erysipelas	1	1	0	0
Mastoiditis	2	2	0	0
Osteomyelitis	1	1	0	0
Pansinusitis	1	1	0	0
	11	10	1	0
Staphylococcic and beta hemolytic streptococcus infections				
Burns	2	1	1	0
Mastoiditis	4	4	0	0
Wound infections	2	1	0	1
	8	6	1	1
Anaerobic cellulitis				
Clostridium welchi	2	2	0	0
	2	2	0	0
Lung abscess				
Putrid	2	0	0	2
Pyogenic	2	2	0	0
	4	2	0	2
Intraperitoneal infections				
Appendical	3	1	1	1
Subphrenic abscess	2	1	0	1
Peritonitis, unknown cause	1	0	0	1
	6	2	1	3
Infections with unproved or unknown etiology				
Pyodermia	1	1	0	0
Cellulitis of leg	1	1	0	0
Pansinusitis	1	1	0	0
Osteomyelitis of tarsus	2	2	0	0
Osteomyelitis of mandible	1	1	0	0
Atypical pneumonia	1	0	1	0
Meningitis	3	2	1	0
Postoperative pneumonitis	1	1	0	0
Perinephric abscess	1	1	0	0
Scarlet fever	1	0	0	1
Arthritis, knee	1	1	0	0
Rheumatic fever	1	0	0	1
Submental abscess	1	1	0	0
Iridocyclitis	1	0	0	1
Choroiditis	1	0	0	1
Multiple sinuses	1	0	0	1
	19	12	2	5
Septic compound fractures				
Staphylococcus	30	26	0	4
Staphylococcic arthritis	2	2	0	0
Staphylococcus and beta hemolytic streptococcus	13	12	0	1
Putrid	2	2	0	0
	47	42	0	5
Miscellaneous infections				
Actinomycosis	4	4	0	0
Malaria (Plasmodium vivax)	4	0	0	4
Chronic ulcerative colitis	2	0	0	2
Coccidiosis	1	0	0	1
Pneumococcic meningitis	1	1	0	0
Pyelonephritis (nonhemolytic streptococcus)	1	1	0	0
Conjunctivitis (Koch-Weeks)	1	1	0	0
	14	7	0	7
	209	164	13	32

Staphylococcic Infections Without Bacteremia.—Sixty-nine, or 87 per cent, of 79 patients showed a favorable response to penicillin therapy. One patient with third degree burns died. The cause of death was not apparent at autopsy, but the clinical record is one of persistent hypotension following curettage of the wounds without blood transfusion. The two failures recorded under mastoiditis were instances of the development of penicillin resistance by the etiologic strains.

Osteomyelitis due to staphylococci deserves special comment. Eleven of twelve infections were reported improved as judged by sterilization of pus and complete or partial healing of sinuses. Three patients treated at Halloran General Hospital had osteomyelitis of the femur. A patient with Brodie's abscess and an abscess of the popliteal space was given systemic penicillin after a pure culture of staphylococcus was obtained at the site of spontaneous rupture of the soft parts abscess. The inflammation subsided rapidly, and on the fourth day of treatment the femur was saucerized and the wound closed around a rubber tissue drain. All subsequent cultures were sterile, the wick was removed on the fifth day and the wound healed and has remained healed for two months. A similar experience was recorded in the treatment of a cortical lesion of the shaft with subperiosteal abscess formation. A third patient was treated with penicillin through a period of acute osteomyelitis of the entire shaft of the femur. Symptomatic recovery with demineralization and new bone formation occurred. The patient was kept under observation and three months later developed an extensive medullary abscess. The entire femur was saucerized and the wound was closed without drainage. Positive cultures were obtained from the pus recovered at operation, but a sterile culture was recovered from a small amount of hematoma evacuated on the tenth postoperative day. At the present time it seems likely that the penicillin therapy of chronic staphylococcic osteomyelitis of the long bones may require surgical intervention with incomplete or primary closure of the wound. Two cases of osteomyelitis of the tarsus in which there was response to penicillin therapy without suppuration are recorded under "infections of unknown etiology." In 1 of the cases already discussed there were spontaneous subsidence and healing of a focus of osteomyelitis in the sacrum. Similar spontaneous and rapid healing of osteomyelitis of the vertebra has been observed with penicillin in cases not included in this series. There is reason to believe that penicillin may effect subsidence of osteomyelitis of flat bones without surgical intervention in the absence of sequestrums.

Hemolytic Streptococcus Infections Without Bacteremia.—Satisfactory bacteriologic sterilization was achieved in every case. One death resulted from pulmonary edema as a complication of the treatment of empyema.

Mixed Staphylococcus and Hemolytic Streptococcus Infections.—One patient with extensive third degree burns died with anuria from a cause not related to penicillin therapy. Six of 8 cases responded favorably and 1 wound infection was not influenced.

Anaerobic Cellulitis.—Two patients with low grade infections of the subcutaneous tissues due to Clostridium perfringens have responded favorably to penicillin therapy.

Lung Abscess.—Penicillin has been without effect on 2 patients with putrid lung abscess; two pyogenic streptococcus lung abscesses were healed.

Intraperitoneal Infections.—Infections arising as complications of appendicitis have not been responsive to treatment, although 1 patient showed improvement coincident with treatment. The series is too small for evaluation.

The response of patients with subphrenic abscess varies with the susceptibility of the causative bacteria.

Miscellaneous Infections.—Malaria due to Plasmodium vivax is not affected by penicillin. In addition to the 4 recorded failures, 2 other patients have developed recurrent malaria under treatment. Four patients with actinomycosis were improved by treatment, but further follow-up is necessary. Chronic ulcerative colitis failed to respond in 2 instances.

III. THERAPY OF CHRONIC INFECTION IN GUNSHOT FRACTURES

The soldier with a chronically infected gunshot fracture presents a complex clinical problem. The degree of nutritional depletion is variable and may be so extreme as to take precedence over all other factors. The bacterial infection is usually polymicrobial and may be latent or active. The anatomic abnormality is irregular, and a wide variety of surgical procedures may be adapted to the proper solution of the problem. Penicillin therapy has a definite place in the management of these cases. Our observations will be recorded in relation to the problems involved:

1. Nutritional depletion.
2. Bacteriologic characteristics of the infection.
3. Selection of cases and surgical management.
4. Results of treatment.

Nutritional Depletion.—The clinical picture of the patient with chronic infection is well known. There is weight loss, diminished strength and muscle mass, anorexia and anemia. Clinical experience with a large group of comparable cases always emphasizes similarities frequently overlooked in the course of contact with individual cases. It seems pertinent to record the observations during this period of treatment with penicillin.

The weight loss has been considerable, varying from 5 to 30 Kg. A loss of 10 Kg. is clinically obvious. Muscle atrophy and loss of strength precede weight loss, and restoration of muscle bulk and strength appear prior to significant weight gain during convalescence.

The distribution of extracellular body fluids has been examined by the sodium thiocyanate [14] and Evans blue

14. Crandall, L. A., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**: 126 (April) 1934.

15. Gregersen, M. I.; Gibson, J. J., and Stead, E. A.: Plasma Volume Determination with Dyes: Errors in Colorimetry; the Use of the Blue Dye T-1824, Am. J. Physiol. **113**: 54 (Sept.) 1935.

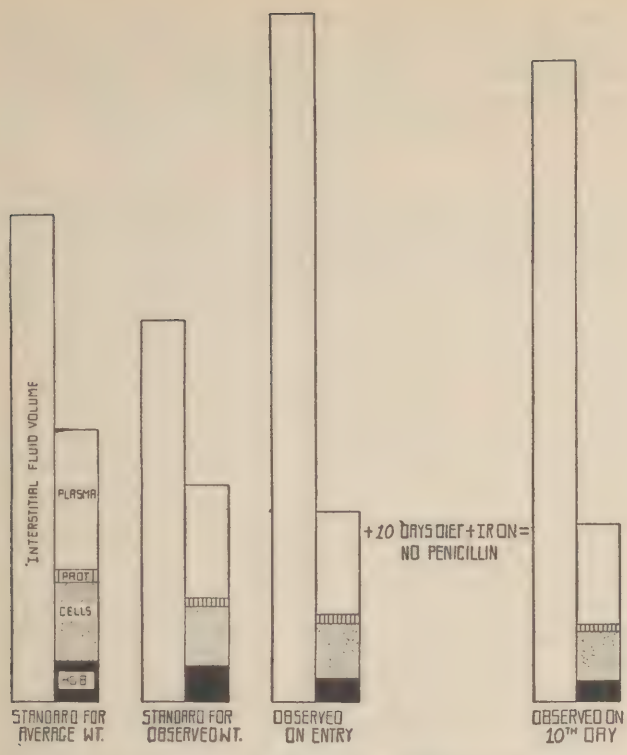

Chart 1.—The interstitial fluid volume was larger than the standard for the observed weight and for the actual weight. The blood volume was less than the standard. The deficit of hemoglobin was greater than indicated by the concentration of hemoglobin as determined in grams per hundred cubic centimeters. This patient was confined to bed with elevation of his infected leg. An abundant diet with added iron was provided. No penicillin, plasma or whole blood was given, and the patient served as a control for the effects of the usual treatment methods. After ten days of known positive nitrogen balance there was a further reduction in blood volume and total grams of hemoglobin.

	Standard		Observed	
	Average Weight	Observed Weight	On Entry	10th Day
Body weight (Kg.)	70	55.1	55.1	54.8
Interstitial fluid volume (cc.)	11,200	8,800	15,800	14.700
Blood volume (cc.)	6,300	5,000	4,400	4,100
Grams hemoglobin per 100 cc.	15	15	13.4	12
Total grams hemoglobin	945	825	545	490
Grams protein per 100 cc.	6.8	6.8	7.6	7.5
Total grams protein	240	190	200	180

dye[15] methods. These findings are presented in charts 1 to 5. On admission to the ward the patients have had an interstitial fluid volume 4 to 7 liters too great for the standard of the patient's observed weight and significantly larger than the standard for the weight prior to injury. During convalescence the interstitial fluid volume slowly decreases without apparent diuresis. The sedimentation rate has been correlated more closely with improvement than any other laboratory determination. Progressive weight gain is rarely apparent before the sixth to the eighth week of convalescence.

Significant fluctuations in the concentration of serum protein and hemoglobin have been recorded. These have been correlated with changes in blood volume and are independent of penicillin therapy. During periods of hemoconcentration the urine volume may equal or exceed the fluid intake. Unless the blood volume is known, a single observation of the concentration of the serum protein or hemoglobin may be misleading. Reductions of 1,500 to 2,000 cc. in blood volume have been recorded. This degree of reduced blood volume is dangerous if it exists at the time of operation because minor blood loss may produce an ineffective blood volume and shock.

Charts 1 to 5 demonstrate also that there is a deficit in the total quantity of circulating hemoglobin and that there is a normal or nearly normal quantity of plasma protein present. Fractionation of the serum proteins into albumin and globulin by the ammonium sulfate method in 30 cases has failed to show any significant variation from accepted normal values. The plasma fibrinogens have been constantly elevated. There have been no abnormalities of the blood electrolytes. It appears that the major deficiency in these chronically infected battle casualties is hemoglobin. This deficiency is frequently masked by hemoconcentration and normal or near normal quantities of hemoglobin in a given unit of blood. Accurate values may be obtained only by calculation of the total circulating hemoglobin when the blood volume and concentration are both known. The practical difficulties of routine blood volume determinations preclude routine use of the method. From a clinical point of view it must be assumed that every patient with chronic infection is anemic.

Liver function has not been specifically investigated. Prothrombin times have invariably been normal. With normal serum proteins and increased fibrinogen values it has been assumed that liver function is satisfactory.

Penicillin therapy does not appear to have any specific effect on the metabolic balance of nitrogen, calcium or phosphorus (table 2).

In this series of patients it has been found that the urinary nitrogen tends to be high (15 to 20 Gm. daily) without increased values for urinary potassium. Positive nitrogen balance is attained by any method that provides an intake of 130 Gm. of protein or more per day. One of the important consequences of penicillin therapy is the improved appetite. Intakes of 150 to 200 Gm. of protein are relatively easily achieved during treatment.

Observations of nitrogen balance have been made for periods of two to six weeks on 15 patients. Two standard diets have been given to provide 2,500 calories for smaller patients and 3,000 calories for larger patients. The general composition of the diet has been 60 per cent carbohydrate, 20 to 25 per cent protein and 15 to 20 per cent fat. With the exception of 2 patients with acute infections, this diet produced a positive nitrogen balance independently of penicillin therapy. On the other hand, positivity of nitrogen balance was not associated with restoration of hemoglobin values unless penicillin was given. The extraordinary virtue of penicillin in this regard is shown in charts 1 and 2. Further studies relating positive nitrogen balance to the rate of hemoglobin formation and hemopoietic activity are clearly indicated.

Patients subjected to operation without supportive intravenous supplement have been studied carefully after operation. The hematocrit, hemoglobin and plasma protein values are relatively unchanged, but the pulse rate is accelerated during the first forty-eight hours. On the third or fourth postoperative day there is a decrease in the hematocrit and hemoglobin values with

an unchanged or increased plasma protein concentration. These changes are illustrated in charts 3 and 4. The blood volume is greatly reduced and there is a disproportionate reduction in the total quantity of hemoglobin as compared to the total quantity of plasma protein. It has not been possible to determine whether this is due to preferential utilization of hemoglobin, less rapid synthesis of new hemoglobin or faulty red cell regeneration. The implications for clinical therapy are clearly for whole blood instead of plasma. The quantitative aspects of replacement therapy to prevent these changes are shown in chart 5.

We have briefly reviewed the results of an extensive investigation of the nutritional status of battle casualties with chronic sepsis as they arrive in this country and after treatment with plasma and sulfonamides. The most apparently deficient substance is hemoglobin, and the interstitial fluid volume is large. Penicillin therapy does not alter nitrogen balance per se but does favor a positive balance in consequence of an improved appetite with controlled infection. Effective restoration of hemoglobin does not result from positive nitrogen balance unless penicillin is given to control infection. However, the rate of metabolic regeneration fails to keep pace with the clinical program made possible by the rapid control of the infection. Frequent transfusions of 500 to 1,000 cc. of whole blood are necessary during the preoperative and postoperative periods. A judicious combination of whole blood and plasma in 1,000 cc. quantities on the day before operation, the day of operation and the day after operation is necessary to maintain blood volume and positive nitrogen balance. Similar quantities of whole blood are necessary once or twice a week until hemoglobin values are restored and maintained at a level of 15 to 16 Gm. per hundred cubic centimeters. It should be remembered constantly that the dietary intake alone may fail to meet the reparative demands of the penicillin program.

Bacteriologic Characteristics of the Infection.—Forty-six cases of septic gunshot fracture have been the subject of extensive aerobic and anaerobic bacteriologic study. The majority of the wounds have proved to be a bacteriologic garden, but it has been possible to define four main types of infection. These are listed according to incidence:

(*a*) Putrid.
(*b*) Staphylococcus.
(*c*) Hemolytic streptococcus.
(*d*) Pseudomonas (pyocyaneus).

Putrid Wound Infection.—This produces dirty malodorous wounds. The etiologic flora is mixed and there may be some synergistic relationship on the part of the involved bacteria. Functionally the infection is proteolytic and attacks dead tissue, devitalized bone fragments, ischemic or avascular muscle and blood clot. In a sense these bacteria are wound scavengers of potential pathogenicity in wounds with extensive tissue destruction or ischemia from closure under tension. The attribute of proteolysis has clinical and bacteriologic significance. The breakdown of an organic protein matrix leads to the foul odor and the release of organically bound sulfur. Hydrogen sulfide is formed and, in the presence of iron, black iron sulfide is produced. Clinically there is frequently a distinct odor of hydrogen sulfide, and hemoglobin is blackened. In the laboratory, diagnosis depends on the digestion

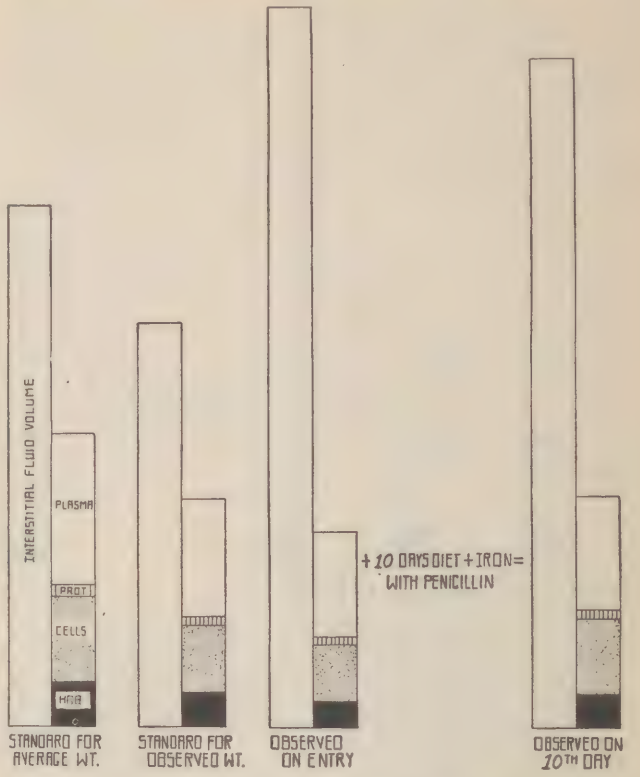

Chart 2.—This chart is to be compared with chart 1. Systemic penicillin therapy has supplemented treatment of a similar infection. An abundant diet with added iron was given, but there were no blood or plasma transfusions. The positivity of nitrogen balance was comparable to that recorded in chart 1. Attention is directed to the initially reduced blood volume and total hemoglobin with restoration of normal values during the period of treatment. The increased interstitial fluid volume was not altered significantly.

	Standard		Observed	
	Average Weight	Observed Weight	On Entry	10th Day
Body weight (Kg.)	75	58.3	58.3	58.3
Interstitial fluid volume (cc.)	12,000	9,300	16,600	15,400
Blood volume (cc.)	6,750	5,250	4,500	5,300
Grams hemoglobin per 100 cc.	15	15	13.2	14.5
Total grams hemoglobin	1,010	790	600	765
Grams protein per 100 cc.	6.8	6.8	6.7	7.5
Total grams protein	255	200	175	210

of meat particles or casein and the detection of sulfur released from sulfur containing amino acids.

The mixed flora includes proteolytic clostridia, microaerophilic and anaerobic nonhemolytic streptococci and Proteus.

The clostridia are predominantly of the sporogenes, bifermentans and tetanomorphum groups (the "fecal anaerobes" of World War I). In vitro studies have shown the sporogenes and bifermentans clostridia to be relatively resistant to penicillin, but they are inhibited by four to five times the effective dose for staphylococci. The tetanomorphum clostridia are as sensitive as the hemolytic streptococci. All these organisms are difficult to remove completely from a wound. Spore forms are as sensitive as the vegetative forms of any given species.

The nonhemolytic streptococci are isolated most easily by anaerobic culture. The thermophilic and heat resistant strains of the faecalis group are generally insensitive to penicillin. The mesophilic and heat sensitive strains are as susceptible as hemolytic streptococci.

The Proteus group of bacteria has shown a preponderance of mirabilis and morganii strains. In 17 of 18 instances of Proteus infection the bacteria have been present in association with proteolytic clostridia. Proteus is not sensitive to penicillin.

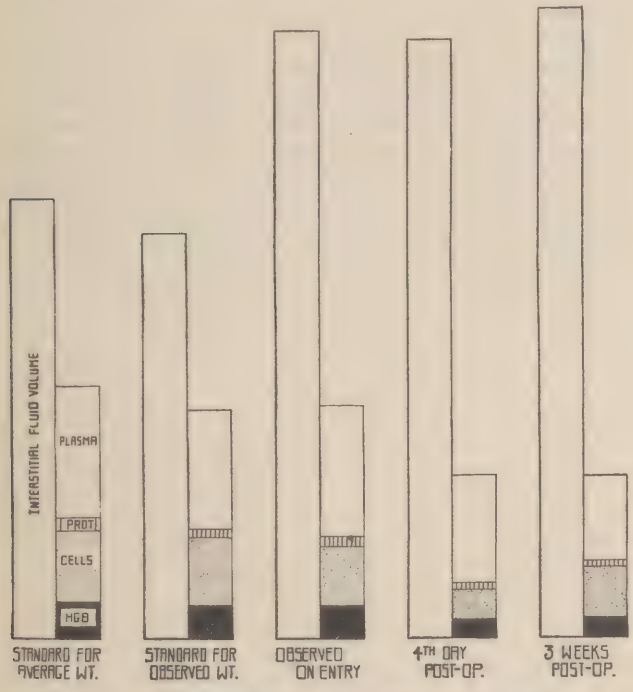

Chart 3.—This patient entered with normal blood values and an increased interstitial fluid volume. Penicillin was given to control active infection without blood or plasma. On the fourth day after operative reduction of fractured metatarsals with sequestrectomy under a tourniquet, the studies were repeated. The hemoglobin concentration fell to 12.8 Gm. per hundred cubic centimeters; the plasma protein rose to 7.4 Gm. per hundred cubic centimeters in consequence of hemoconcentration and a greater decrease in hemoglobin. It is significant that this hemoconcentration was accomplished without reduction of an excessive interstitial fluid volume. The nitrogen balance was negative throughout this period. The values recorded at three weeks after operation emphasize the slow rate of metabolic regeneration in the absence of supportive transfusions with whole blood.

	Standard		Observed		
	Average Weight	Observed Weight	On Entry	4th Day Post-operatively	3 Weeks Post-operatively
Body weight (Kg.)	64	57.6	57.6	57.9	59
Interstitial fluid volume (cc.)	10,000	9,200	13,800	13,600	14,300
Blood volume (cc.)	5,750	5,200	5,300	3,700	3,650
Grams hemoglobin per 100 cc.	15	15	14.5	12.8	13.2
Total grams hemoglobin	860	780	770	420	480
Grams protein per 100 cc.	6.8	6.8	6.9	7.4	7.4
Total grams protein	220	195	220	165	155

The presence of proteolytic putrid infection was demonstrated in 34, or 74 per cent, of 46 cases (table 3). Bacteriologic demonstration of proteolysis has been more helpful than species identification in the clinical management of putrid wound infection.

Staphylococcic Infection.—This was the second most prevalent complication. Coagulase positive staphylococci were present in 30, or 65 per cent, of 46 cases.

Beta Hemolytic Streptococcus Infection.—These were isolated from 15, or 33 per cent, of 46 patients. All except 1 of these patients had received prophylactic sulfonamide therapy. Nine received local and systemic chemotherapy, 4 only systemic, and 1 only local. The serologic groups of these strains is shown in table 4. No strain was completely resistant to penicillin therapy, but in 3 cases the strains persisted in diminished numbers in the wound until sequestrectomy was performed. There was no instance of a pure hemolytic streptococcus infection.

Pyocyaneus.—This organism was recovered in 12, or 26 per cent, of the 46 cases. Never the only etiologic organism, it frequently became predominant in the treated wounds. The abundant and intensely bluish green pus of these late wounds is almost a feature of penicillin therapy and has some diagnostic value. When the dressing is green on the surface and brown in the depths of the wound it can be assumed that anaerobic conditions were produced in consequence of improper packing. Pyocyaneus seems to thrive in the wound under treatment with penicillin. Its presence has not interfered with successful skin grafting or secondary closure of extensive defects.

The foregoing patterns of infection exist in combination (table 5). The response to penicillin therapy may be predicted fairly accurately in accordance with the susceptibility of the various infecting organisms, as shown in table 6. There has been no opportunity to conduct significant observations on the organisms of gas gangrene.

Staphylococcic and beta hemolytic streptococcus infections are controlled satisfactorily with few exceptions. When these bacteria are predominant, penicillin therapy induces a prompt subsidence of cellulitis and inflammatory edema, a diminution in the quantity of pus and a mucoid character of the exudate. This "penicillin effect" correlates with the disappearance of the bacteria on smear and culture of the pus. Cultures of sequestrums removed during treatment are often negative for streptococci but positive for staphylococci. Seventy per cent of the total of 46 wounds harbored bacteria of one or both of these susceptible species.

Pyocyaneus has a high nuisance value and may retard wound healing without causing any real concern.

The paramount problem in the penicillin therapy of septic gunshot fractures is putrid wound infection. It has been impossible to remove these organisms completely from wounds. There is a patent discrepancy between in vitro and in vivo results in many cases. A combination of systemic and local therapy will abolish fever and initiate clinical improvement in patients with pure putrid infections. In such instances suppuration continues until sequestrectomy is performed. The association of putrid wound infection with retained fragments of devitalized bone or foreign bodies is constant. After surgical trauma the infecton flares up temporarily as the bacteria gain a foothold in the damaged tissue and blood clot of the wound. Attempts at partial or complete wound closure invite anaerobic cellulitis. Operative sequestrectomy should be per-

formed with minimal trauma, and no exposed cortical bone should be left in the wound. Local therapy should be continued until the wound is healed to prevent secondary staphylococcic infection. The pus of such secondary infection provides an acceptable medium for the growth of proteolytic bacteria. Penicillin therapy must be supplemented with meticulous local care of the wound when putrid infection is present.

Gram Negative Bacilli.—Gram negative bacilli of the colon, paracolon, Aerobacter and para-Aerobacter groups have been inconstant and transient contaminants of the wound. They rarely persist for more than a week in a properly managed wound. The air of the dressing room has been found to be a source of such contamination. These bacteria have been below the level of clinical significance.

Selection of Cases and Surgical Management.—It is necessary to have a definite program for the primary selection and subsequent management of all surgical patients. The presence of infection presents no diagnostic problem, but it has been recognized that infection may be latent or active. Activity of infection has been evaluated in terms of fever, cellulitis or gross suppuration.

The presence of sequestrums or retained foreign bodies is almost universal in these patients. Metallic missile fragments are not a frequent source of chronic suppuration. Bits of clothing, particles of concrete from land mines and other débris have been a fairly constant source of suppuration persistent during treatment. Sequestrums have been sterilized of streptococci but continued to harbor staphylococci, clostridia, Proteus and Pyocyaneus in spite of local therapy. Sequestrectomy and the removal of foreign bodies are an essential part of an effective penicillin program.

Septic arthritis, uncomplicated by foreign bodies in the joint, responds dramatically. Local therapy is an effective supplement in the management of this complication. In some instances the plan of repeated aspiration and injection of penicillin has been followed. In other cases it seemed preferable to establish surgical drainage without actually placing drains in the joint cavity. Sequestrums or foreign bodies in the joint have required removal.

These observations have established operative procedures as part of the program and made it necessary to define a schedule of penicillin therapy in relation to operative intervention. The patients have been divided into four groups:

Group 1. Latent infection and no nutritional depletion.
Group 2. Latent infection with nutritional depletion.
Group 3. Active infection with no nutritional depletion.
Group 4. Active infection with nutritional depletion.

Nutritional depletion is estimated in terms of weight loss, general appearance of the patient and anemia.

Patients in group 1 with latent infection and no nutritional depletion receive no preliminary therapy. Penicillin is reserved for those cases which present postoperative exacerbations of infection. In a few patients with staphylococcic or mixed staphylococcic and hemolytic strepticoccus infection, penicillin has been tried as a prophylactic measure to permit bone graftings or platings with primary closure. These cases have been carefully selected, and the results warrant a cautious expansion of such practice.

Patients in group 2 with latent infection and nutritional depletion profit by a period of supervised diet and repeated blood transfusions. The decision to use or withhold penicillin has been variable in accordance with clinical opinion and the predominant bacterial pathogen in the wound.

Patients in group 3 with active infection and no nutritional depletion usually represent instances of acute infection. As such, they are candidates for immediate therapy.

Patients in group 4 with active infection and severe nutritional depletion comprise the majority of patients under treatment. By and large, replacement therapy with diet, iron and whole blood is more effective when penicillin is used to control the infection. The timing of operation depends on the efficacy of the supportive program. Three to five days of penicillin and trans-

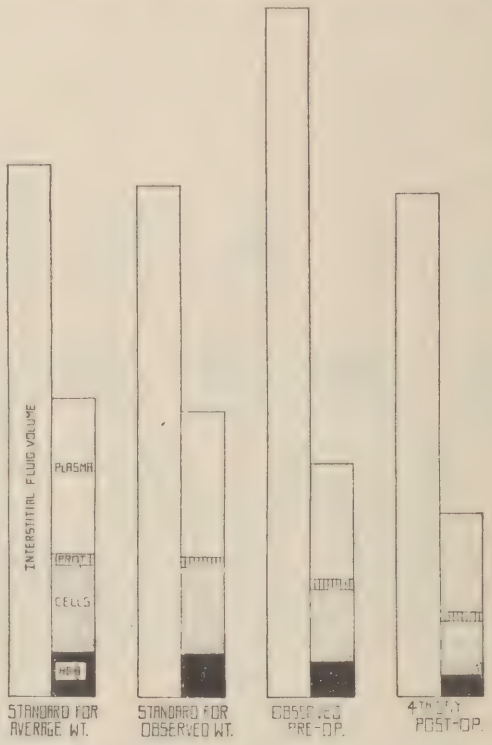

Chart 4.—This chart is to be compared with chart 3. The patient received penicillin without supportive transfusions. A compound fracture was reduced and plated. The initial concentration of hemoglobin was nearly normal; the blood volume was reduced. After operation there was a further diminution in blood volume with a definite decrease in hemoglobin. The significant feature of the study was the observation that a loss of 4,300 cc. from the interstitial fluid volume was recorded coincidentally. It is argued that an available interstitial fluid may buffer the reduction of blood volume without preventing critical deficit in the hemoglobin fraction.

	Standard		Observed	
	Average Weight	Observed Weight	On Entry	4th Day Post-operatively
Body weight (Kg.)	77	72.8	72.8	71.7
Interstitial fluid volume (cc.)	12,300	11,700	15,900	11,600
Blood volume (cc.)	6,900	6,600	5,400	4,250
Grams hemoglobin per 100 cc	15	15	14.5	11.7
Total grams hemoglobin	1,035	990	810	500
Grams protein per 100 cc	6.8	6.8	8.0	7.5
Total grams protein	260	245	232	190

fusion therapy is often sufficient to prepare the patient for the indicated operation. For a few patients a week to ten days of preparation has seemed valuable.

Postoperatively it is important to maintain nitrogen balance. This can be done by supplying 130 Gm. of protein daily. In most cases intravenous therapy is necessary to maintain this intake on the day of operation and the first postoperative day. Plasma supplies 7 Gm. of protein per hundred cubic centimeters, whereas whole blood supplies more nearly 18 Gm. per hundred cubic centimeters. It can be seen that this protein requirement is met by 2 liters of plasma, 750 cc. of whole blood or a mixture of 500 cc. of whole blood and 500 cc. of plasma. The greater need for hemoglobin has been emphasized, and there is an increasing preference for whole blood. Transfusion therapy is continued during the phase of convalescence to maintain blood volume, hemoglobin and red cell values.

Patients with closed wounds and an uneventful convalescence have received penicillin systemically for eight to ten days. The management of the open wound has been variable. Removal of the pack in the first five days leads to wound hemorrhage, putrid wound infection of the blood clot and contamination with air

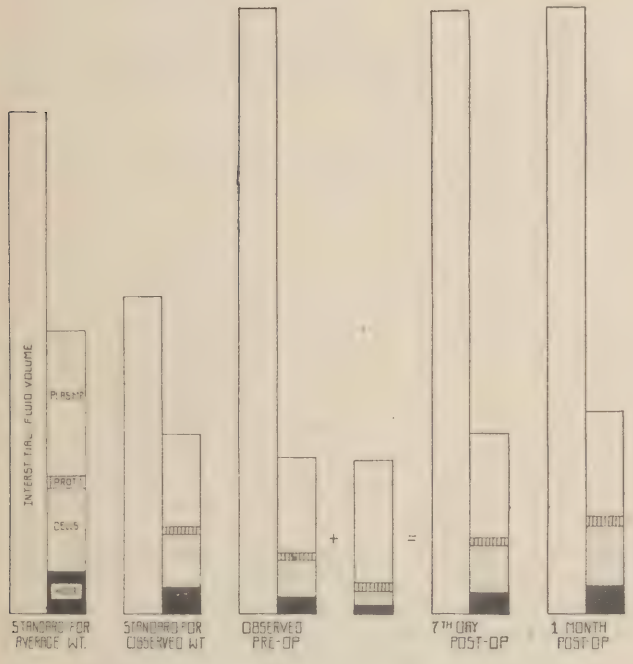

Chart 5.—This chart should be compared with charts 3 and 4. It is designed to show the measure of benefit from 1,500 cc. of whole blood and 2,500 cc. of plasma, a total of 4,000 cc. given over a three day period in relation to sequestrectomy. The blood volume was increased to a standard normal value, but 1,500 cc. of whole blood did not raise the total hemoglobin value to a normal level. The total deficit would have been met more effectively by the use of a total of 2,500 cc. of whole blood than by the mixture of blood and plasma. The interstitial fluid volume remained unchanged throughout this period. The increase in blood volume one month after operation is due entirely to an increase in cells with an unchanged plasma volume; the hematocrit has returned to normal.

	Standard		Observed			
	Average Weight	Observed Weight	On Entry	Given as Transfusions	7th Day Postoperatively	1 Month Postoperatively
Body weight (Kg.).....	82	52.1	52.1	4,000 cc.	52	
Interstitial fluid volume (cc.).....	13,100	8,300	15,800	.....	15,700	15,800
Blood volume (cc.)....	7,400	4,700	4,100	.....	4,700	5,300
Grams hemoglobin per 100 cc.....	15	15	11	.....	12.2	13.8
Total grams hemoglobin.....	1,100	705	450	225	575	730
Grams protein per 100 cc.....	6.8	6.8	7.2	.....	6.6	7.22
Total grams protein...	280	175	195	220	190	215

borne gram negative bacilli. Immediate irrigation of the operative wound with penicillin introduced through inlying tubes may prolong the period of postoperative bleeding. At the present time systemic penicillin therapy is continued for five to seven days. The wound is then dressed and gently cleansed with hydrogen peroxide to remove blood clot and devitalized tissue fragments. Gauze is saturated with salt solution containing 250 units of penicillin per cubic centimeter and gently placed in the wound under a seal of gauze impregnated with ointment. Systemic penicillin is usually discontinued at this time if subsequent daily dressings are feasible. Some form of therapy must be continued until all bare bone is covered with healthy granulation tissue. Local therapy is preferable whenever practical because it is more economical than systemic therapy. A high local concentration is particularly useful to reduce the intensity of infection with proteolytic clostridia.

Results of Treatment.—Table 7 records the results of penicillin therapy in 45 cases of septic compound fractures. Forty, or 88 per cent, showed improvement in consequence of treatment. Sequestrectomy was performed in 34 of the 40 "improved" cases, whereas no operation was performed in the 5 failures (table 8). One of the 5 failures ultimately came to amputation of the foot for extensive osteomyelitis of the entire tarsus. Complete wound healing is known to have occurred in 25 of the 40 successful cases, and the wound was clean and granulating at the time of the report in 13 others. Of the 6 cases in which improvement occurred without sequestrectomy, recurrent infection in a previously healed wound subsequently developed in 2.

A review of the data sheets reveals the fact that the scarcity of penicillin has led to its use for only the more seriously infected patients with extensive anatomic defects. The period between penicillin therapy of the infection and complete wound healing may be considerable. The results as given for the 45 patients followed through to wound healing are substantiated by the clinical progress of 20 other patients incompletely healed at the present time. It is significant that no death has resulted from this early correction of the infected fractures. The importance of the studies to date lies in the demonstration that penicillin permits active surgical intervention almost immediately. Many of the patients reported as healed will require reconstructive operations. It is premature to draw any conclusions as to the role of penicillin in such a program. The incidence of late recurrence of infection

cannot be predicted. The need for continued observation of these patients is recognized.

SUMMARY

For the routine systemic administration of penicillin there is a preference for the intramuscular route. Intravenous therapy is used for the constant administration of the drug in cases of immediately life endangering infections. In the treatment of meningitis, penicillin has been injected into the lumbar space, the cistern and the ventricles. Systemic therapy has been used initially. Local therapy has been supplemental and effective in those wounds appropriate for topical therapy. In many cases a short period of systemic therapy has been followed by local treatment of an operative wound.

It is premature to attempt a precise definition of dosage. The quality and potency of penicillin are still showing rapid improvement. A safe average dose for streptococcic and similarly sensitive bacterial infections is about 90,000 units per day given in divided doses intramuscularly every four hours. Staphylococcic infections require 200,000 to 400,000 units daily given in divided doses every three hours intramuscularly. Solutions for local therapy containing 250 units per cubic centimeter have been satisfactory.

The untoward reactions attributable to penicillin are analogous to the syndrome of serum sickness. Urticarial reactions have been noted in approximately 5 per cent of the cases and have occurred as a complication of local therapy without parenteral penicillin. The urticaria may appear after the first dose or as long as nine days after the last dose. It appears equally frequently in the various weeks of treatment. Fever and, more rarely, abdominal cramps may appear with urticaria. Fever with dermatographia and no urticaria has been seen. These reactions suggest a form of sensitization, but tests for sensitivity are negative. Treatment can be continued usually through the three to five day period of urticaria with subsidence of the reaction. There is no evidence of permanent sensitization to penicillin.

The results in the treatment of acute infections due to staphylococci and the sulfonamide resistant streptococci are additional proof that penicillin is an exceptionally potent antibacterial agent. The inability of the drug to control staphylococcic endocarditis has been confirmed. Evidence is accumulating that surgical intervention is often necessary in the penicillin therapy of staphylococcic osteomyelitis of the long bones, whereas a more conservative program is warranted in infections of the flat bones. Temporary improvement has been recorded during brief periods of treatment in actinomycotic infections. In general, the response to therapy is conditioned by the susceptibility of the infecting organism and the pathologic anatomy of the inflammatory process.

Particular emphasis has been given in this report to the usefulness of penicillin in the immediate management of septic gunshot fractures. When susceptible bacteria predominate in a wound there is prompt improvement during treatment with recurrence later. This recurrence is due to sequestrums or foreign bodies and the inability of penicillin to sterilize such foci of infection. Surgical intervention is necessary in most instances. Operations on patients with chronic infections are notorious for their incidence of shock, anoxic complications and prolonged convalescence. It is not surprising that this investigative program has been concerned with intensive operative preparation and postoperative care.

The "unsteady state" of these patients has been related to a reduced blood volume, a deficiency of the total circulating and available hemoglobin and an excessive interstitial fluid volume.

The blood volume is always small in relation to the standard, but considerable fluctuation in the actual

TABLE 2.—*Metabolic Balance as Affected by Penicillin Therapy in a Convalescent Patient*

	Period 1—6 Days No Penicillin	Period 2—6 Days With Penicillin
Intake in grams		
Calcium	0.88	0.88
Phosphorus	5.33	5.33
Nitrogen	70.2	70.2
Urine output in grams		
Calcium	2.29	2.40
Phosphorus	4.85	4.82
Nitrogen	63.6	61.9
Urine volume in cc	11,518	11,145
Stool output in grams		
Calcium	1.42	1.28
Phosphorus	2.14	1.73
Nitrogen	12.7	11.5
Total output in grams		
Calcium	3.71	3.68
Phosphorus	6.99	6.55
Nitrogen	76.3	73.4
Metabolic balance		
Calcium	−2.83	−2.80
Phosphorus	−1.66	−1.22
Nitrogen	−6.1	−3.2

TABLE 3.—*Analysis of Bacterial Flora in 34 Cases of Putrid Infection in Septic Gunshot Fractures*

1. Proteolytic clostridia		32
2. Proteus bacilli		18*
3. Nonhemolytic streptococci		19
a. Mesophilic	6	
b. Thermophilic	9	
c. Mixed	4	

* Proteus bacilli were present with clostridia in 17 cases.

TABLE 4.—*Serologic Grouping of Beta Hemolytic Streptococci*

Group A	6	Not group A, B, C	4
Group B	0	Not tested	4
Group C	1		—
Total			15

TABLE 5.—*Bacteriology of Septic Gunshot Fractures*

Type of Infection	Number of Cases
Putrid only	4
+ Staphylococcus	9
+ Staphylococcus and hemolytic streptococcus	5
+ Pyocyaneus	5
+ Staphylococcus, hemolytic streptococcus and pyocyaneus	5
+ Staphylococcus and pyocyaneus	4
+ Hemolytic streptococcus	2
+ Hemolytic streptococcus and pyocyaneus	0
Staphylococcus only	4
+ Hemolytic streptococcus	1
+ Pyocyaneus	1
+ Hemolytic streptococcus and pyocyaneus	1
Hemolytic streptococcus only	0
+ Pyocyaneus	1
Pyocyaneus only	0
Total	46
Putrid infections	34, or 74%
Staphylococcic infections	30, or 65%
Hemolytic streptococcus infections	15, or 33%
Pyocyaneus infections	12, or 26%

size of the blood volume occurs without apparent cause. Such a finding is not surprising in view of the increased interstitial fluid volume. During these phases of hemoconcentration and hemodilution there is considerable variation in the concentration of red cells, hematocrit, hemoglobin and serum protein. The usual laboratory findings show wide discrepancies from day to day unless they are interpreted in terms of total circulating quantities on the basis of a known blood volume.

A positive nitrogen balance may be established by an adequate diet alone, but restoration of hemoglobin values demands effective control of the infection. Penicillin therapy is associated with an improved appetite and effective repair of hemoglobin deficits. The rate of metabolic regeneration is too slow to keep pace with the needs of an operative program, however, and economy of penicillin and hospitalization requires a supplemental source of hemoglobin. Whole blood meets this demand more effectively than plasma. The quantity is formidable. It is estimated that 1,500 to 3,000 cc. of blood per patient is necessary.

TABLE 6.—*Response to Penicillin*

Type of Infection	Penicillin Response	
	Systemic	Local
I. Putrid		
1. Proteolytic clostridia	+ (large dosage)	+
2. Proteus bacilli	0	0
3. Nonhemolytic streptococcus		
a. Mesophilic	+	+
b. Thermophilic (Strep. faecalis)	0	0 (or slight)
II. Staphylococcus	+ (3-5 days)	+ (often necessary)
III. Hemolytic streptococcus	+ (1-3 days)	+ (not essential)
IV. Pseudomonas (pyocyaneus)	0	0

The bacteria present in the wounds are variously susceptible to penicillin and are important limiting factors in the choice of operative procedure in a given case. The staphylococci and hemolytic streptococci can be controlled effectively in the great majority of instances. Pyocyaneus is not inhibited and has a high nuisance value but rarely does more than delay wound healing. The proteolytic bacteria of putrid wound infection are present in three fourths of the cases.

TABLE 7.—*Results of Treatment of Septic Compound Fractures**

Site	No. of Cases	Improved	Died	No Effect
Femur	17	13	0	4
Lower leg	12	12	0	0
Foot and ankle	8	7	0	1
Upper extremity	7	7	0	0
Skull	1	1	0	0
	45	40	0	5

* This series is composed of cases followed for a sufficient period of time to allow evaluation and should be distinguished from the group of 46 cases reported in the bacteriologic analysis.

Anaerobic cellulitis is favorably influenced by penicillin given systemically in large doses. High concentrations of locally applied drug are necessary for the maximal inhibition of the proteolytic clostridia and the nonhemolytic streptococci. Proteus and the faecalis groups of streptococci are insensitive to penicillin. Putrid wound infection is a contraindication to extensive surgical revision or primary wound closure even when penicillin is given.

The results in the treatment of septic gunshot fractures indicate that dramatically successful results may be achieved by the meticulous surgeon who combines penicillin, effective blood transfusions and conservative surgical procedures into a program of thoughtful management of individual cases.

CONCLUSIONS

1. Penicillin has been administered intravenously, intramuscularly, intrathecally and locally. The indications for each of these routes have been established.

2. The untoward complications noted in this series have been limited to urticaria and other reactions suggesting an analogy to serum sickness. The reactions are transient during therapy and there is no permanent sensitization. No significantly harmful effects have been observed.

3. Penicillin is an effective antibacterial agent in the treatment of acute infections caused by staphylococci, hemolytic and nonhemolytic streptococci, mixed infections due to gram-positive bacteria and actinomycosis. The gram negative diplococci are susceptible to treatment. Gram negative bacilli are resistant. Mixed infections with both gram positive and gram negative bacteria may be benefited through the effect on the susceptible bacterial species. Malaria has not been controlled by penicillin.

4. An intensive investigation of the clinical status of patients with chronically infected gunshot fractures

TABLE 8.—*Relation of Sequestrectomy to Result of Penicillin Therapy*

	Number of Cases	Sequestrectomy
Improved	40	34
No effect	5	0

has revealed a major deficiency of red blood cells and hemoglobin. Positive nitrogen balance may be established in the presence of continuing infection, but the synthesis of new tissue proteins and the regeneration of red cells and hemoglobin are dependent on control of the infection. The dramatic effectiveness of penicillin in rapidly establishing this phase of convalescence is added proof of the unique position of the drug among antibacterial agents. The normal rate of hemoglobin regeneration is not surpassed, and whole blood transfusion therapy is necessary.

5. The polymicrobial character of septic gunshot fractures has been defined in terms of putrid wound infection, staphylococcic infection, hemolytic streptococcus infection and Pyocyaneus infection. Staphylococci and streptococci are rapidly responsive to therapy. Anaerobic cellulitis due to the proteolytid bacteria of putrid wound infection responds to penicillin, but the bacteria may persist in the presence of devitalized tissue or wound exudates. Pyocyaneus is not susceptible to penicillin and is relatively unimportant as a single pathogen in the surgical management of the wound.

6. Penicillin therapy permits a direct and immediate surgical approach to the management of septic gunshot fractures. Its role in this regard is analogous to the use of vitamin K for patients with obstructive jaundice. Such a concept emphasizes the limitations of penicillin therapy and designates the supplemental position of penicillin in the overall surgical program.

notes

PENICILLIUM INOCULATED SURGICAL DRESSINGS

Since purified penicillin is not generally available for civilian use, attempts have been made to find a substitute. One suggestion is the use of moist penicillium inoculated surgical dressings, which have been tested clinically by Robinson and Wallace [1] of the Allegheny General Hospital. In the preparation of such dressings, eight layers of gauze were placed in a Petri dish and saturated with a medium containing 1 per cent yeast extract, 2 per cent dextrose, 2 per cent corn starch and 2 per cent glycerin. The dish was then autoclaved, inoculated with penicillium and incubated at room temperature. Two days later 1 cc. of sterile human plasma was allowed to flush underneath the dressing to simulate its application to an open wound. At intervals the Petri dish was tipped so that a small amount of fluid would drain away. Titration of this fluid showed a rapid production of penicillin in the gauze culture. The maximum titer was reached by the end of six days, at which time the drainage fluid inhibited growth of test strains of Staphylococcus aureus in dilutions as high as 1 : 200. The titer decreased rapidly after the seventh day. Clinical tests of such penicillium gauze dressings were made on a number of patients. A typical case was one of acute osteomyelitis and periostosis of the right humerus. A previous wide incision had been made over the site of the infection and sulfonamides prescribed without relief. A moist penicillium gauze dressing was placed over the wound, with prompt relief of pain. In ten days the patient was discharged clinically well. Another patient was treated for a large staphylococcic furuncle on the back of the neck and a third for multiple soft tissue Staphylococcus aureus abscesses over the lower back and sacral region with equally favorable results. From these and other clinical data the Pittsburgh surgeons conclude that penicillium inoculated surgical dressings are of promise in the treatment of acute and chronic pyogenic surface infections. Their use is recommended merely as an emergency measure until adequate supplies of purified penicillin are generally available. Whether or not there are toxic or allergic reactions that might limit the use of such dressings has not yet been reported.

1. Robinson, G H., and Wallace, J. E.: Science **98**: 329 (Oct. 8) 1943.

specific illnesses

COMBINED PENICILLIN AND HEPARIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

REPORT OF SEVEN CONSECUTIVE SUCCESSFULLY TREATED PATIENTS

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In experimental thrombotic bacterial endocarditis [1] the disappearance of vegetations requires the use of a suitable chemotherapeutic agent and an anticoagulant. The clinical application of this principle in subacute bacterial endocarditis has been disappointing; the technics of therapy are cumbersome, the toxicity of treatment has been excessive even for an otherwise fatal disease and the successes have been few and irregular.[2] Early efforts made with sulfonamides, with or without heparin, have been mostly abandoned. The introduction of penicillin proved equally disappointing; the commission appointed by the National Research Council has already reported unfavorably and discouraged the use of the at present inadequate supply of the drug for the treatment of viridans endocarditis.[3]

The present report, which deals with the apparently successful treatment of 7 consecutive examples of subacute bacterial endocarditis, employs variations on previous technics. Penicillin [4] is used to replace sulfonamide in the conjoint chemotherapeutic-anticoagulant attack and prolonged heparinization [5] has been accomplished primarily by a special method devised for the subcutaneous deposition of the drug.[6]

CLINICAL MATERIAL

Six of the 7 patients [7] suffered from a bacterial endocarditis that was engrafted on a chronic rheumatic valvulitis, and the other had a congenital cardiac defect. In 5 of the 7 patients the etiologic organism was a Streptococcus viridans; the sixth patient had a hemolytic streptococcus and the seventh a pneumococcus type 27.

TECHNIC OF TREATMENT

Probatory sensitivity tests were performed in each instance. The bacteria were inhibited within the dilution of 0.007 to 0.01 Florey units per cubic centimeter of penicillin. The daily dosage of penicillin varied from 40,000 to 200,000 Florey units and the total ranged from 867,920 to 7,890,340 Florey units. The heparin dosage approximated 300 mg. every second day when given subcutaneously and 200 mg. daily when incorporated in the venoclysis.

Heparinization was checked by the Lee-White modification of Howell's method for determining blood coagulation time.[8] A reading of thirty to sixty minutes was regarded as satisfactory evidence of anticoagulant activity. The present technic has minimal toxicity; it is simple of accomplishment and the immediate results, at least, appear to be uniformly successful.

CASE REVIEWS

CASE 1.—*Subacute bacterial endocarditis, pneumococcus type 27, ten weeks; congenital cardiac anomaly (septal defect); post-therapy, five months, clinically well and blood stream sterile.*

I. Z., a girl aged 7½, was admitted to the Jewish Hospital of Brooklyn on June 3, 1943 because of chills and fever of ten weeks' duration. At the age of 9 months a loud precordial murmur was found on routine physical examination. Three years before admission she had a bout of unexplained fever lasting eight weeks. She remained perfectly well thereafter until ten weeks before admission, when she developed an

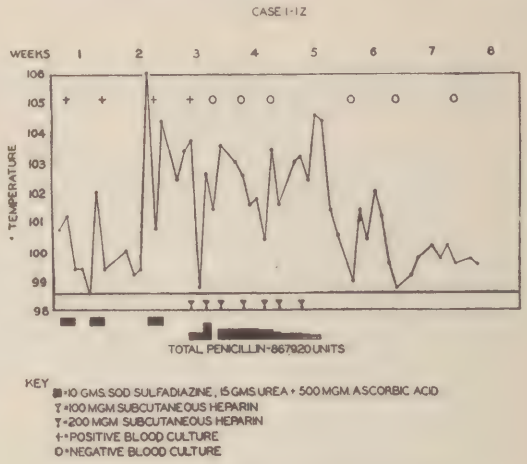

Chart 1.—Temperature and dosage in case 1.

earache and low grade fever lasting three days. Two days after this subsided she suddenly developed a high temperature, which was spiking in character and continuous to the time of admission. She also had intermittent chills. Four weeks prior to hospitalization she developed lobar consolidation (infarct?) which persisted ten days. She lost 13 pounds (6 Kg.) in the last ten days.

On admission the temperature was 103.8 F., pulse 132 and respirations 32. Blood pressure was 110/90. The heart was slightly enlarged to the left, and a loud systolic murmur was heard all over the precordium. The spleen was just palpable on inspiration. The clinical impression was subacute bacterial endocarditis engrafted on a congenital cardiac anomaly (septal defect). Blood culture, taken on June 4, revealed pneumococcus, type 27. Massive sulfonamide therapy [9] was begun

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From the Department of Medicine and the Department of Laboratories, Jewish Hospital.

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2. Kelson, S. R., and White, P. D.: A New Method of Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **113**: 1700-1702 (Nov. 4) 1939. McLean, Jay; Meyer, B. B. M., and Griffith, J. M.: Heparin in Subacute Bacterial Endocarditis, ibid. **117**: 1870-1875 (Nov. 29) 1941.
3. Keefer, C. S.; Blake, F. G.; Marshall, B. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections, J. A. M. A. **122**: 1217-1224 (Aug. 28) 1943.
4. The entire supply of penicillin for this project was obtained from the Charles Pfizer Company of Brooklyn. Mr. J. L. Smith and Dr. W. J. Smith of that organization showed keen interest and close cooperation.
5. Roche-Organon, Inc., Nutley, N. J., supplied all the heparin (Liquaemin) for both the subcutaneous and the intravenous administration of the drug. Drs. Ralph D. Shaner and Leo Pirk of that company were especially cooperative.
6. Loewe, Leo; Rosenblatt, Philip, and Lederer, Max: A New Method of Administering Heparin, Proc. Soc. Exper. Biol. & Med. **50**: 53-55, 1942. Loewe, Leo, and Rosenblatt, Philip: A New Practical Method for Subcutaneous Administration of Heparin, Am. J. M. Sc., to be published.
7. This series of cases was recruited mostly from the medical services of Drs. A. L. Louria, M. A. Rabinowitz, J. Rosenthal and E. L. Shlevin. We wish to thank them for the privilege of utilizing this clinical material.
8. Gradwohl, R. B. H.: Clinical Laboratory Methods, ed. 3, St. Louis, C. V. Mosby Company, 1943, p. 514.
9. Dick, C. F.: Subacute Bacterial Endocarditis, J. A. M. A. **120**: 24-25 (Sept. 5) 1942.

June 4, consisting of 10 Gm. of sodium sulfadiazine, 15 Gm. of urea and 500 mg. of ascorbic acid dissolved in 650 cc. of distilled water administered by venoclysis. Six such courses were given over a period of twelve days without improvement. Blood cultures taken on June 9, 14 and 18 remained positive for pneumococcus type 27. Sulfadiazine blood levels ranged up to 78.8 mg. per hundred cubic centimeters total and 74.2 mg. per hundred cubic centimeters free. In view of the lack of response to this therapy, a combined penicillin-heparin regimen was initiated June 19. The patient received subcutaneous deposits of 100 or 200 mg. of heparin approximately every other day. During the first twenty-four hours, 42,400 Florey units of penicillin dissolved in 2,000 cc. of 5 per cent dextrose in saline solution was given intravenously by slow drip. On June 20 and 21 42,400 and 129,600 units respectively were administered by vein. The venoclysis was then discontinued because the patient became extremely uncooperative. Blood culture on June 21 showed no growth. Although her general condition was good the temperature persisted and it was decided to resume penicillin therapy by the intramuscular route. On June 24 penicillin was again started with 64,800 Florey units in fractional intramuscular dosage. Combined penicillin-heparin therapy was then continued without interruption until July 5, a total of 867,920 units of penicillin and 1,200 mg. heparin being given over a period of sixteen days. On June 27 her temperature, although still elevated, was on a lower level. On June 29 she showed evidence of extensive infarction of the lower two thirds of the right lung. Blood cultures taken on June 28, July 6 and July 19 were sterile. On July 22 her general condition was good, a slight elevation of temperature to about 100 F. being ascribed to a cold which she developed. She was discharged July 23 for further convalescence at home. Since then she has been seen periodically, her temperature remaining normal and the blood cultures negative. She is now attending school regularly.

CASE 2.—*Subacute bacterial endocarditis, Streptococcus viridans, ten months; chronic rheumatic cardiovalvular disease, aortic; no response to massive sulfonamide and three courses of penicillin-heparin therapy; fourth course of penicillin-heparin therapy successfully sterilized blood stream; clinically much improved.*

S. R., a man aged 34, was referred to the Jewish Hospital of Brooklyn by Dr. I. L. Epstein on Feb. 7, 1943 complaining of fever and cough of six weeks' duration. At the age of 13 he had spent two months in bed because of "an inflamed heart chamber" and joint pains. At the time a diagnosis was made of rheumatic heart disease. The patient was well until about six weeks before admission, when he developed a cough followed by persistent low grade fever, which continued despite oral sulfadiazine. There were no physical signs apart from a systolic murmur at the mitral area and a diastolic murmur at the aortic area. The admission diagnosis of subacute bacterial endocarditis was confirmed by blood cultures taken February 10 and 12, both of which were positive for Streptococcus viridans. On February 22 he was given 18 Gm. of sodium sulfapyridine by intravenous drip, which failed to sterilize the blood stream. Supplemental fever therapy through the medium of intravenous triple typhoid vaccine was instituted March 8. Sulfadiazine levels were maintained around 20 mg. per hundred cubic centimeters, and fever treatments were

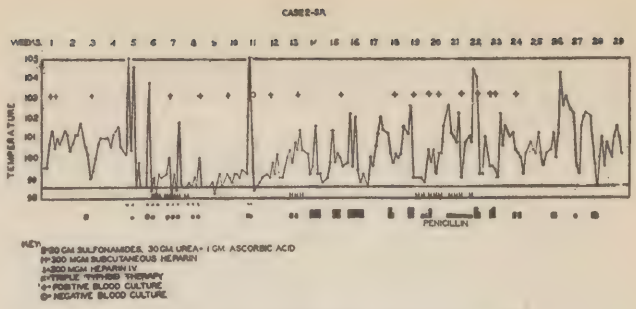

Chart 2.—First twenty-eight weeks in case 2.

given approximately every other day. After three such pyrexia reactions heparin was added to the program. However, on March 23 and April 5 and 14 Streptococcus viridans was recovered from the blood stream despite adequate fever therapy and intensive sulfadiazine medication, which had attained blood levels up to 40 mg. per hundred cubic centimeters. Sulfathiazole-fever therapy was similarly ineffectual. On May 4 massive cyclic intravenous chemotherapy was started with sodium sulfadiazine, the individual dose approaching 40 Gm. Urea and ascorbic acid were frequently employed as adjuvants. Blood levels reached as high as 123 mg. per hundred cubic centimeters total and 109 mg. per hundred cubic centimeters of free sulfadiazine. Despite nineteen such intensive courses of treatment over a period of six weeks the blood cultures on May 22 and on June 9 and 16 were richly positive. On June 19 a three day course of penicillin-heparin therapy was initiated, which was obviously inadequate. When additional penicillin supplies were available on June 27 the patient was started on a nine day schedule comprising approximately 40,000 units of penicillin daily by vein and 300 mg. of heparin deposited every other day under the skin. When the blood cultures remained positive, massive sulfonamide therapy was again projected. From July 7 to August 17 he received variously sodium sulfadiazine, sodium sulfapyridine, sodium sulfathiazole and sodium sulfamerazine without sterilization of the blood stream. On August 27 a more elaborate course of penicillin-heparin therapy was begun with 200,000 units of penicillin daily by venoclysis and 300 mg. of heparin subcutaneously approximately every other day. This was continued for fourteen days, after which the blood cultures remained negative until October 4, when organisms reappeared. The temperature, which had been flat for weeks (charts 2 and 3) now showed some irregularity, and on October 9 a fourth course of penicillin-heparin was initiated. The daily dosage plan consisted of 200,000 units of penicillin and 200 mg. of heparin given together by continuous venoclysis for a period of twenty-four days. The occasional sharp febrile rises due to heparin receded promptly following temporary withdrawal of the drug. Since completion of the therapeutic program the temperature has remained normal with the exception of a slight fever due to a complicating nasopharyngitis. The blood cultures since October 13 have been sterile; the sedimentation rate receded from a high of 130 mm. per hour on June 14 to 10 mm. per hour on November 26 and the patient is in excellent condition. In all, this patient received four courses of combined therapy totaling 7,890,340 Florey units of penicillin and 7,100 mg. o heparin.

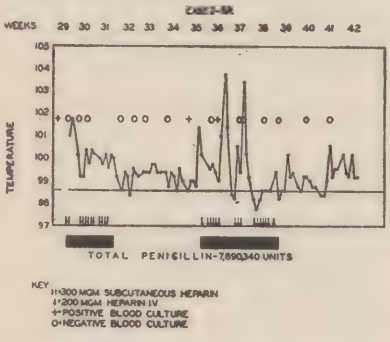

Chart 3. Remainder of course in case 2.

Case 3.—*Subacute bacterial endocarditis, Streptococcus viridans, eight months; chronic rheumatic cardiovalvular disease, mitral and aortic; three cycles of penicillin-heparin therapy; no clinical or laboratory evidence of bacterial activity for four months.*

L. O., a woman aged 24, unmarried, was admitted to the Jewish Hospital of Brooklyn on April 16, 1943. Her first attack of rheumatic fever, of which she had three or four, occurred at the age of 7. Her present illness began in December 1942 with complaints of chills, fever, malaise, pain in the hip and occasional crops of petechiae on the arms. She did not improve with home care and finally entered the Mount Sinai Hospital of Cleveland, where the diagnosis of subacute bacterial endocarditis due to Streptococcus viridans was established. This diagnosis was substantiated, clinically and bacteriologically, at the Jewish Hospital. A rough systolic thrill over the aortic area and systolic and diastolic murmurs, loudest at the base, indicated a predominant aortic valve lesion. There were several petechiae on the fingers. The spleen was not palpable. The patient's condition did not change materially following intensive oral and parenteral administration of sulfadiazine, which achieved blood levels of 41.2 mg. per hundred cubic centimeters total and 37.0 mg. per hundred cubic centimeters free. Fresh petechiae appeared occasionally, and the temperature swung irregularly up to 103 F. From May 17 until July 31, when the penicillin-heparin program was started, she received fifteen courses of sulfadiazine, each treatment comprising 10 to 20 Gm. of sodium sulfadiazine, 15 to 30 Gm. of urea and 0.5 to 1 Gm. of ascorbic acid given together by venoclysis. The complete lack of response, clinical and bacteriologic, to this massive chemotherapy justified the adoption of the penicillin-heparin regimen. The initial course of the latter lasted for nine days and consisted of 60,000 to 100,000 units of penicillin daily by continuous venoclysis and 100 or 200 mg. of heparin subcutaneously approximately every other

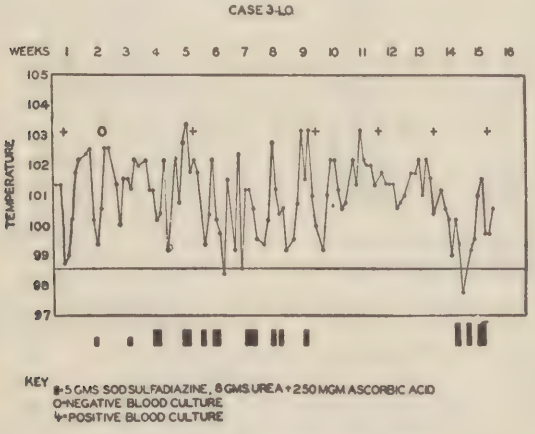

Chart 4.—First fifteen weeks in case 3.

day. The irregular temperature, up to 101 F. during therapy, was attributable in part to the heparin. Repeated blood cultures taken on August 9, 12, 16, 20 and 24 were all sterile. When the patient continued subfebrile, however, additional treatment was projected. The dosage schedule of penicillin was 100,000 units daily for fourteen days. Collateral heparinization was started with 300 mg. and continued with 200 mg. subcutaneously every other day. On September 1 there was a definite febrile reaction which was due to a grossly contaminated penicillin solution. Although blood cultures taken August 28 and September 3 and 12 were reported sterile, the temperature, which had been normal, became slightly elevated to 100 F. A third course of penicillin and heparin seemed indicated and was begun on September 20, the penicillin dosage being increased to 200,000 units daily intravenously for twenty-eight consecutive days. Satisfactory heparinization was maintained with 200 mg. of heparin incorporated daily with the penicillin except when eliminated temporarily because of an inordinate febrile response or excessive anticoagulant activity.

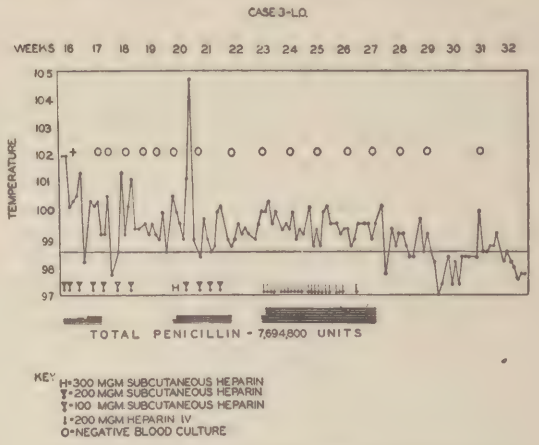

Chart 5.—Sixteenth to thirty-second weeks in case 3.

Dental consultation[10] on October 5 revealed the presence of advanced foci of infection and on October 13 several teeth were removed which were definitely diseased. Gauze packing saturated with penicillin solution, 5,000 units per cubic centimeter, was applied topically. Streptococcus viridans was recovered from the dental sockets.

The patient withstood the operative procedure well and all therapy was discontinued on October 19, five days after operation. Blood cultures taken on September 20 and 27, October 4, 12, 13, 18 and 25 and November 1 were all sterile and the temperature continued normal. The patient's weight has increased from a low of 71 pounds (32 Kg.) on July 10 to 92 pounds (42 Kg.). The patient received a total of 7,694,800 Florey units of penicillin in three cycles, 700,000, 1,400,000 and 5,594,800 units respectively. The overall total of heparin employed was 6,700 mg.

Case 4.—*Subacute bacterial endocarditis, Streptococcus viridans, three weeks; chronic rheumatic cardiovalvular disease, mitral and aortic; post-therapy cerebral embolization with complete recovery; no clinical or laboratory evidence of bacterial activity, three months.*

J. N., a man aged 31, was admitted to the Jewish Hospital of Brooklyn on Aug. 17, 1943 because of unexplained fever of three weeks' duration. He had rheumatic fever at the age of 6 and about ten to fifteen years ago noticed dyspnea on exertion, which has persisted to date. Three weeks prior to admission the patient developed pain, redness and tenderness of the toes of his right foot, followed in a week by fever and headache. Two days prior to hospitalization he experienced pain in the left upper quadrant. He suffered a weight loss of 5 pounds (2.3 Kg.).

On entrance his temperature was 98.2 F., pulse 120, respirations 24 and blood pressure 140/0. There were petechiae

10. The oral surgery on these patients was performed by Dr. M. D. Levin, attending oral surgeon of the Jewish Hospital.

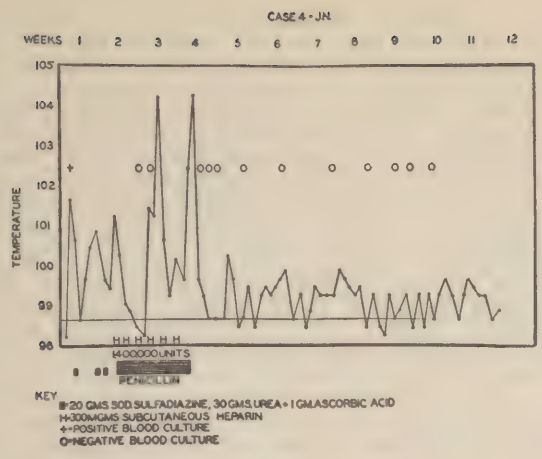

Chart 6.—Course in case 4.

in the buccal mucosa. The heart was enlarged to the anterior axillary line. The first mitral sound was loud and snapping followed by a blowing systolic murmur; the second sound was blurred. There was a to and fro murmur at the aortic area transmitted to the neck, which obliterated the basal sounds. The spleen was palpable 3 fingerbreadths below the costal margin. The clinical impression was rheumatic heart disease with aortic stenosis and insufficiency, mitral insufficiency and subacute bacterial endocarditis with splenic infarction. Blood culture on the day of admission yielded 100 to 200 colonies of Streptococcus viridans per plate. On three separate occasions, August 19, 23 and 24, the patient was given intravenously by the gravity method 20 Gm. of sodium sulfadiazine, 30 Gm. of urea and 1 Gm. of ascorbic acid dissolved in 1,500 cc. of distilled water, all of which was wholly ineffectual. Furthermore, he reacted badly to this form of therapy, so that a penicillin-heparin regimen was instituted on August 26. The latter consisted of the daily administration of 100,000 Florey units of penicillin by continuous intravenous drip in conjunction with 300 mg. of heparin subcutaneously on alternate days. The temperature, which was irregularly elevated during the two weeks course of treatment, reached normal two days following its suspension. On September 14 the patient developed a complete left hemiplegia, which cleared entirely within four days. In view of the persistently negative blood cultures it was assumed that the embolization was abacterial. There were no further untoward events until his discharge on November 3, the temperature remained normal, the splenomegaly disappeared, the sedimentation rate fell from 95 mm. per hour on September 13 to 14 mm. per hour on October 18, and blood cultures done at practically weekly intervals up to and including October 25 were all sterile. His general condition at discharge was most satisfactory. His weight, which on admission was 145 pounds (66 Kg.), increased to 159 pounds (72 Kg.) on October 31.

As a precautionary measure a dental survey was done on October 19. Several foci of infection were found and the offending teeth removed. Ten thousand units of penicillin dissolved in 2 cc. of saline solution was injected intramuscularly every three hours on the day before, the day of and the day after the oral surgery. The operative site was packed with gauze dipped in 5 cc. of saline solution containing 20,000 units of penicillin. There was no febrile reaction, and the blood culture taken one hour after the dental extraction was sterile. Streptococcus viridans was recovered from cultures of the teeth.

In all, the patient received 1,400,000 Florey units of penicillin over a period of fourteen days, during which time he was also given 1,800 mg of heparin.

Case 5.—*Subacute bacterial endocarditis, Streptococcus viridans, four months; chronic rheumatic cardiovalvular disease, mitral; no response to intensive sulfonamide and initial course of penicillin-heparin therapy; second twenty-eight day cycle of penicillin-heparin therapy effected sterilization of blood stream and progressive clinical improvement, which has persisted two and a half months; possible penicillin-heparin sensitization.*

C. M., a woman aged 22, married, was admitted to the Jewish Hospital of Brooklyn Aug. 17, 1943 because of "bacteria in the blood stream" of three months' duration. She had rheumatic fever at the ages of 6 and 9½ years, after which she was known to have a heart murmur. She was well until May 4, 1943, when she had the "grip," from which she recovered except for weakness and lethargy. About a week later she experienced sudden severe sacral and right lumbar pain, which was followed by ten days of hematuria. She subsequently had left upper quadrant pain which lasted one week. In the seventh week of her illness she was delivered of a 7 month infant under caudal anesthesia. Chills and fever recurred frequently, and blood cultures continued positive despite intensive sulfonamide therapy.

On admission the skin presented a pale lemon yellow pallor with a slight malar flush. There were no petechiae. The spleen was palpable 2 fingerbreadths below the costal margin. The heart was enlarged, and there was a rumbling to and

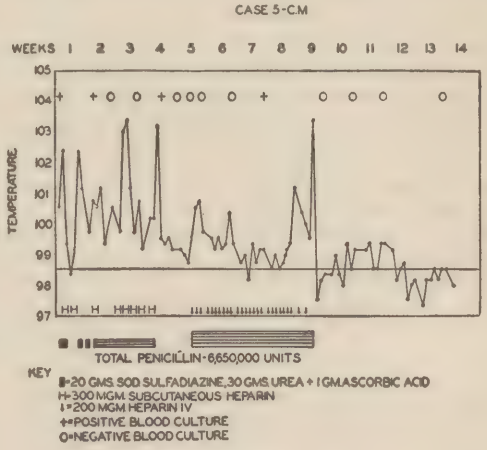

Chart 7.—Course in case 5

fro murmur at the apex. There was a diastolic murmur at Erb's point. Blood culture taken on the day of admission revealed 250 to 350 colonies of Streptococcus viridans per plate. Chemotherapy was given by vein on August 8, 19, 23 and 24 in the form of sodium sulfadiazine 20 Gm., urea 30 Gm. and ascorbic acid 1 Gm. dissolved in 1,000 cc. of distilled water in combination with heparin. The latter was administered subcutaneously in 300 mg doses. All this proved unavailing, as the elevated temperature persisted and the blood culture on August 25 was positive. Accordingly penicillin-heparin therapy was started on August 26 with 100,000 units of the former daily by continuous venoclysis for fourteen days and 300 mg. of the latter subcutaneously approximately every other day. The temperature dropped with the onset of this regimen, ranging between 99.2 and 101 F. with the exception of an abrupt rise to 104 F. due to air borne contaminants in the penicillin solution. The rise in temperature on the day following suspension of the therapy was attributed to the heparin deposited the preceding day. In view of the continued irregular temperature despite the sterile blood cultures on September 12 and 17 following the positive one of September 10, additional penicillin-heparin therapy was projected. The daily dosage schedule begun on September 18 and continued uninterruptedly for twenty-eight days consisted of 200,000 Florey units of

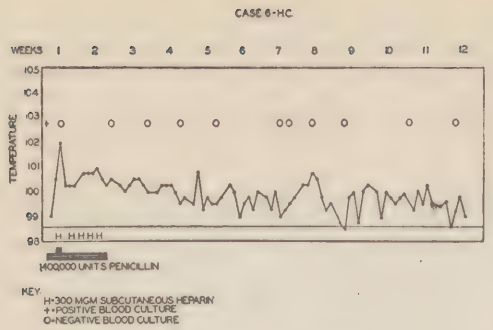

Chart 8.—Course in case 6.

penicillin and 200 mg. of heparin given in combination by continuous intravenous drip. During the therapy the general condition of the patient was good in spite of irregular persistent elevation of temperature. A blood culture taken on October 4 was reported positive for Enterococcus haemolyticus, for which no valid explanation was forthcoming because the temperature was normal and the patient appeared exceptionally well. On the twentieth day of therapy, October 12, the temperature suddenly rose to 104 F. An occasional rale was heard at the left base and, on the premise that bronchopneumonia was developing, sulfadiazine 1.5 Gm. was administered every four hours. Blood culture taken this day was sterile, however, and with no further progress in the physical signs the temperature continued spiking daily for four days, attaining a level of 105 F. on the twenty-seventh day of therapy. Penicillin-heparin sensitization was suspected and all treatment stopped, following which the temperature promptly fell to normal within twenty-four hours and remained so thereafter. Blood cultures taken on October 18 and 25 and November 15 were sterile and the sedimentation rate dropped from 67 mm. per hour on September 13 to 12 mm. per hour on November 15. On October 27 two devitalized teeth were removed with the customary prophylactic penicillin treatment (see case 4). The patient was allowed out of bed on November 3 and discharged in excellent condition on November 17. Her weight increased from 105 pounds (48 Kg.) on September 12 to 120 pounds (54 Kg.) on November 14.

This patient received two courses of penicillin-heparin therapy, one of fourteen days' and the other of twenty-eight days' duration; the penicillin requirements were 1,400,000 and 5,250,000 Florey units respectively. The total of heparin employed was 7,600 mg.

CASE 6.—*Subacute bacterial endocarditis, Streptococcus haemolyticus, three weeks; chronic rheumatic cardiovalvular disease, aortic; widespread, almost lethal, embolizations; prompt, dramatic response to penicillin-heparin therapy; progressive clinical improvement and negative blood cultures, three months.*

H. C., a woman aged 52, unmarried, was admitted to the Jewish Hospital of Brooklyn on Aug. 28, 1943 for penicillin-heparin therapy. She was transferred for this purpose from the St. Elizabeth Hospital of New York with a diagnosis of streptococcus (hemolytic) bacterial endocarditis engrafted on a chronic rheumatic cardiovalvular defect. She entered the St. Elizabeth Hospital on August 7 because of pain in the chest and upper abdomen, sudden weakness, general malaise and chills and fever of one day's duration. She was acutely ill and had two petechiae in the right conjunctival sac. The harsh systolic murmur over the aortic area and the diminished second aortic sound were indicative of an aortic stenotic lesion. The blood pressure was 104/60. Streptococcus haemolyticus was isolated from the throat on August 9 and from the blood on August 12. Intensive oral and parenteral sulfonamide therapy had no influence on the course of the infection, the clinical condition becoming progressively more critical with repeated embolizations and hyperpyrexia.

On admission to the Jewish Hospital she was virtually moribund. There was complete motor and sensory aphasia in addition to splinter hemorrhages under the nail beds of the toes and fingers and small ecchymotic areas on the volar surfaces of the fingers. Gallop rhythm was present, with heart sounds of poor quality. Blood culture on August 28 revealed 130 colonies of Streptococcus haemolyticus per plate. Penicillin therapy was started immediately, the dosage plan being 100,000 Florey units daily for thirteen days with the exception of the third day, when she received 200,000 units. Heparin, which was withheld pending the outcome of the recent cerebral embolization, was subsequently administered by the subcutaneous method, 300 mg. every other day on five occasions for a total of 1,500 mg. The sterile blood culture on August 31 and the reduction of temperature mirrored the dramatic clinical improvement. Toward the end of the second week of therapy the patient showed signs of pulmonary edema and, in view of the absence of bacterial activity, it was felt that the therapy could safely be interrupted. The patient was digitalized and fluid intake limited. During the succeeding four weeks her condition progressively improved, all embolic phenomena disappeared, the temperature ranged between 99 and 100 F., and blood cultures taken approximately at weekly intervals were sterile.

Occasional complaints of toothache prompted a dental survey at this time, which disclosed several badly diseased teeth. A two stage removal of these foci of infection was done under the customary precautionary penicillin regimen (see case 4).

The sedimentation rate dropped from 30 mm. per hour on September 2 to 14 mm. per hour on October 25 and routine periodic blood cultures were sterile. The clinical improvement continued satisfactorily, the temperature, which hovered between 99.4 and 100.2 F. for several weeks finally became normal, and the patient was discharged in good condition on November 17.

CASE 7.—*Subacute bacterial endocarditis. Streptococcus viridans, ten weeks; chronic rheumatic cardiovalvular disease, mitral; repeated, cyclic, massive sulfonamide therapy unavailing; satisfactory response to a two weeks course of penicillin-heparin therapy; progressive clinical improvement and complete absence of bacterial activity over two months; post-therapy, prophylactic tonsillectomy.*

I. S., a man aged 35, was admitted to the Jewish Hospital of Brooklyn on Aug. 8, 1943 with complaints of chills and fever of ten weeks' duration. On the tenth day of his illness he had sudden, sharp, severe left upper quadrant pain, which receded after twenty-four hours. He entered another hospital, where a provisional diagnosis of typhoid was made. He was told that he had a large spleen but that all laboratory tests, including blood cultures, had been negative. He remained in the hospital for three weeks, the last ten days of which were afebrile.

Two weeks before admission to the Jewish Hospital the patient began to have chills and fever with daily spiking of temperature. His past history revealed an episode of "rheumatism for two months" at the age of 5. On entrance the temperature was 100.6 F., pulse 120, respirations 30 and blood pressure 120/80. The skin was pale with slight café au lait tint. There was a systolic blowing murmur at the apex, and the spleen was palpable 2 fingerbreadths below the costal margin. Blood culture done the day of admission revealed 40 colonies of Streptococcus viridans per cubic centimeter and confirmed the clinical diagnosis of subacute bacterial endocarditis. On August 11 combined sulfonamide-heparin therapy was started. The chemotherapy was of the massive, cyclic variety and consisted of 20 to 40 Gm. of sodium sulfadiazine, 30 to 60 Gm. of Zeitz filtered urea and 1 to 2 Gm. of ascorbic acid given on two successive days at approximately weekly intervals. Heparinization was accomplished with 300 mg. of the drug given subcutaneously approximately every other day. After the second cycle of therapy the blood culture taken during a post-transfusional febrile reaction yielded 7 to 12 colonies of Streptococcus haemolyticus per plate. The fifth and sixth cycles of chemotherapy (60 Gm. of sodium sulfadiazine) were started on September 10 and 17 without effect, as

the blood cultures taken on September 14, 15 and 20 were all variously positive for Streptococcus viridans. It was evident at this point that the organisms were sulfonamide resistant and that massive chemotherapy had been futile despite levels up to 68.7 mg. per hundred cubic centimeters total and 59.0 mg. per hundred cubic centimeters free sulfadiazine.

On September 26 a fourteen day course of penicillin-heparin was started, the daily dosage consisting of about 200,000 Florey units of penicillin and 200 mg. of heparin dissolved in 1,500 cc. of isotonic solution of sodium chloride and given by continuous intravenous drip. The total penicillin administered was 3,203,200 Florey units, and the overall total of heparin was 6,700 mg. The temperature, which was irregularly lower during therapy, promptly dropped to normal following cessation of therapy on October 10 and has remained so to date.

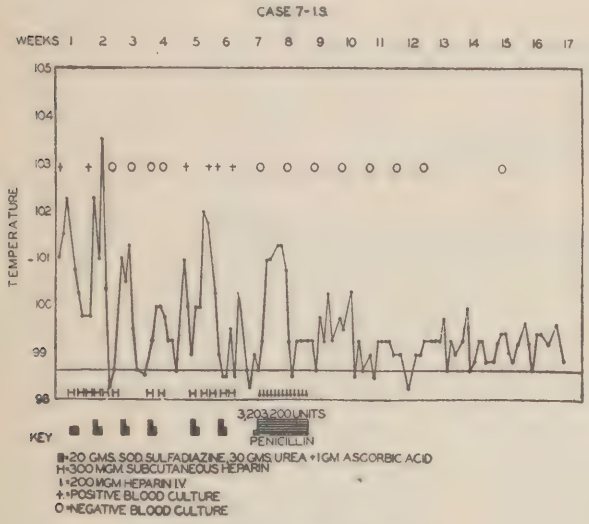

Chart 9.—Course in case 7.

The sedimentation rate receded from 100 mm. per hour on August 9 to 24 mm. per hour on November 15, and repeated blood cultures have been sterile. The weight has increased from 143 pounds (65 Kg.) on September 12 to 153 pounds (69 Kg.) on November 21. The patient is in excellent condition and is awaiting discharge following the removal on November 22 of frankly infected tonsils, from which pus could be extruded. The prophylactic tonsillectomy was done under the customary, precautionary penicillin regimen (see case 4) Streptococcus viridans was the predominant organism in cultures of the removed tonsils.

SUMMARY

1. Seven consecutive patients with subacute bacterial endocarditis have been treated by a method which combines the uses of penicillin and heparin. Further observation will be required to determine the permanence of results, but the immediate effects suggest uniformly successful sterilization of the blood and relief of clinical manifestations.

2. Penicillin has been given in requisite dosage by the method of the continuous intravenous drip. One patient, however, also received the drug intramuscularly.

3. Heparin has been deposited subcutaneously in most instances but was occasionally given in the intravenous infusion.

4. There has been no significant toxicity as the direct result of therapy. In point of fact, treatment was well tolerated and each of the patients exhibited striking well-being during and after the active period of treatment.

5. In a few of the patients the efficacy of the therapy may have been enhanced by the preliminary use of sulfonamide.

6. Post-therapy management included the removal of possible foci in the teeth and nasopharynx. These surgical procedures were accompanied by additional prophylactic chemotherapy with penicillin.

notes

11

THE TREATMENT OF LOBAR PNEUMONIA AND PNEUMOCOCCAL EMPYEMA WITH PENICILLIN*

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THE therapeutic value of penicillin for patients was first described in the treatment of cases of staphylococcal infection.[1] Even though penicillin has not been found in tests in the laboratory to be as potent in antibacterial action against staphylococci as against pneumococci or hemolytic streptococci, it is, nevertheless, more effective against staphylococci than are the sulfonamide drugs. Consequently, the fact that clinical trials were first attempted in cases of severe staphylococcal sepsis constituted a rational procedure and subsequent experience has yielded highly satisfactory results in this type of infection that has not been uniformly amenable to sulfonamide therapy.[1,2,3]

In accord with experimental studies which have demonstrated the antagonistic action of penicillin against a wide variety of pathogenic bacterial species, estimates of the value of penicillin therapy have been broadened beyond cases of staphylococcal etiology to include many different kinds of infection in man. The most recent results have been recorded and summarized in the comprehensive report of Keefer, Blake, Marshall, Lockwood, and Wood.[3]

The present report is limited to a description of the results obtained in the treatment of pneumococcal pneumonia and pneumococcal empyema with penicillin.

The unusually high degree of antibacterial activity of penicillin, *in vitro*, against pneumococci was demonstrated in the original report of Fleming[4] and has been repeatedly observed by others.[5,6,7] *In vivo*, the curative action of penicillin in mice has been demonstrated against many

* The investigation of empyema was aided through the Commission on Pneumonia, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of The Surgeon General, United States Army.
Read November 4, 1943 before the Stated Meeting of The New York Academy of Medicine.

hundred thousand lethal doses of highly virulent strains of different serological types of pneumococci.[8,9] Although some variation in the sensitivity of strains has been suggested, pneumococci appear to be one of the pathogenic bacterial species most vulnerable to the action of penicillin.

When the experimental results just mentioned are taken into account in connection with the proven low toxicity of penicillin for man, the favorable outcome of the treatment of pneumococcal infections with penicillin becomes a reasonable expectancy.

Forty-six cases of pneumococcal pneumonia and 8 cases of pneumococcal empyema comprise the present series. In view of the fact that the methods of treatment and the details of the study of the cases of pneumonia and of the cases of empyema were different, each of the subjects is presented separately.

I. The Treatment of Pneumococcal Pneumonia with Penicillin

Although the number (46) cases of pneumonia is not great, the selection of patients to be treated with penicillin was limited to those who, on admission, exhibited lobar consolidation and a degree of severity indicating the probable pneumococcal etiology of the infection. Even though therapy was at times instituted before the bacteriology was reported there were only three instances in which the specific etiology was undetermined. The data in Table I on the distribution of serological types of pneumococci responsible for the infections and also the incidence of bacteriemia indicate that the cases used for treatment consisted of a representative sample of pneumococcal pneumonia with respect to kind and severity.

In the patients with pneumonia the observations have been directed not only toward determining the value of penicillin as an effective curative agent but the attempt has also been made to estimate the range of dosage that was sufficient without constantly employing amounts that might be excessive and, therefore, unnecessary. For this latter purpose the number of injections and the duration of treatment were arbitrarily altered in order to observe the response to limited treatment.

Material and Route of Administration. The penicillin was supplied in a dry powder contained in sealed ampoules. It was kept constantly in the ice box. Solutions for injection when prepared in advance were also kept in refrigeration but were not retained for longer than a day

or two. It may be noted in passing that solutions used in the laboratory for experimental purposes have been found to retain potency for several weeks.

Penicillin in solution was given to patients by repeated injections either intravenously or intramuscularly. For intravenous injection the powder was dissolved in physiological salt solution or sterile water in the ratio of 1000 units to 1-1.5 cc. of solution. For intramuscular injection the ratio was 1000 units to 0.3 cc. of solution so that the usual individual dose of 10,000 units was contained in a total volume of 3.0 cc.

Some of the patients were treated solely by intravenous injections, others only by intramuscular injections, and still others received intravenous medication for the first few doses followed by intramuscular injections for subsequent treatments. The intramuscular route proved to be effective and was, for convenience sake, frequently employed. However, in cases which appeared seriously ill on admission, one to four injections were given intravenously and when improvement seemed evident subsequent injections were given intramuscularly.

Dosage of Penicillin and Spacing of Treatment. The amount of penicillin per dose ranged from 10,000 to 25,000 units, most frequently the former. The repeated doses which were given in series were made at three hour intervals.

Several procedures were employed which differed in the following respects:

1. Number of repeated injections at three hourly intervals which comprised one series of treatments. The single series varied from three to eight injections, the latter lasting for twenty-four hours.

2. The lapses between each series of injections which were given from day to day were not always kept constant. Charts are presented which illustrate the clinical courses of patients who received interrupted treatment.

3. The number of consecutive days of treatment varied from one to four. The information which emerged from altering the duration of treatment will be subsequently discussed.

Etiological Pneumococcal Types. From Table I it may be noted that in 32 (69 per cent) of the cases the infecting pneumococci belonged to serological Types I–VIII. Fourteen patients had bacteriemia (30 per cent). Among the cases in which the pneumonia was due to pneumococci, Types I–VIII, 13 (40 per cent) has bacteriemia.

TABLE I

SUMMARY OF CASES OF PNEUMONIA TREATED WITH PENICILLIN

Pneumo Types	*No. of Cases*	*Blood Culture*		*Duration of Treatment Days*				*Total Dosage of Penicillin (Range) Oxford Units*	*Response*		
		+	—	1	2	3	4		*Definite*	*Indefinite*	*Died*
I	11	4	7		2	5	3	60,000-250,000 Av: 148,000	10		1
II	6	3	3		1	3	2	70,000-170,000 Av: 113,000	6		
III	1	1	0				1	140,000	1		
IV	1	1	0			1		110,000	1		
V	5	1	4		1	2	2	70,000-190,000 Av. 115,000	4	1	
VII	2	1	1		1		1	70,000-140,000 Av: 105,000	2		
VIII	4	2	2	1		2	1	70,000-120,000 Av. 90,000	3		1
IX	1	0	1			1		120,000			1
XI	2	0	2	1			1	40,000-130,000 Av: 85,000	2		
XII	1	0	1			1		90,000	1		
XV	1	0	1			1		120,000	1		
XIX	1	0	1			1		90,000	1		
XX	1	1	0		1			50,000	1		
XXIX	1	0	1			1		95,000		1	
Unclass.	7	0	7	2	1	3	1	30,000-160,000 Av: 100,000	5	2	
TOTAL	45	14	31	4	7	21	12	30,000-250,000 Av. 105,000	38	4	3

Outcome of Treatment. Among the 46 patients treated with penicillin, three died. (Mortality 6.5 per cent). Of the patients who died, one was a 69 year old man who had severe congestive heart failure together with pneumonia and bacteriemia due to pneumococcus, Type VIII. His blood culture, taken on the second hospital day, was sterile and his temperature was below 100°F. but the heart failure was worse. He died 36 hours after admission. The second fatal case had pneumonia and bacteriemia, pneumococcus, Type I, superimposed on some chronic pulmonary disease. His blood culture of the second hospital day was sterile but there was no clinical improvement. Subsequent therapy included sulfadiazine and antipneumococcus serum, Type I, but it was ineffectual. The third fatal case had pneumonia due to pneumococcus, Type I, but no bacteriemia. He did not appear severely ill but did not respond to penicillin. He died on the third hospital day a few hours after pulmonary edema developed.

Of the 43 patients who recovered, in four instances therapy was not followed by rapid clinical recovery. The result is, therefore, listed as indefinite, although the final diagnosis in one patient was primary atypical pneumonia and the other three had prolonged courses, in one of whom there was delayed resolution which was unexplained; in another, who after several weeks developed pneumothorax, tuberculosis was suspected; and the third patient had bronchiectasis on which the pneumonia was superimposed. Even though these three latter cases are classed as ineffectively treated, the sterilization of the bacteriemia by penicillin in two of them will be subsequently mentioned.

The remaining 39 patients (84 per cent) recovered in a manner that indicated the high degree of effectiveness of penicillin.

The rapidity in the drop in temperature was striking, the change occurring usually within the first 12 to 20 hours, and the impression was that the response occurred somewhat more quickly than that observed after sulfonamide therapy. The alleviation of symptoms was marked. The respirations were slowed to normal rates coincident with improvement although cough persisted for several days. There were no untoward depressive physiological reactions referable to the rapid critical change in the condition of the patients. Although no data have been collected with regard to the rate with which clearing of the consolidated area occurred, the impression has been formed that resolution progressed more rapidly than that observed following sulfonamide therapy.

The leukocyte count was unaffected by penicillin and returned to normal within four to six days.

No toxic reactions were observed, except an occasional pyrogenic reaction which came on about one hour after an injection and lasted approximately two hours. The degree of soreness at the site of intramuscular injection was never severe, nor was there any swelling or redness or appreciable local irritation.

The hematopoietic system exhibited no signs of irritation. No special changes in urine were noted. No psychic or neurological abnormalities were evident.

Duration of Treatment. From an analysis of the data given in Table I under the heading "Duration of Treatment, Days," information is available concerning the length of time that therapy may be required. In all of the patients without complications an initial definite response was noted within 16 to 20 hours of beginning treatment as evidenced by sharp drop in temperature and symptomatic improvement. The subsequent course varied, however, depending on the length of time treatment was continued.

From Table I it may be seen that most of the patients, 31, were treated for 3 to 4 days. Among this group, when no complicating factors existed, the initial improvement persisted as permanent cure.

The complications which delayed prompt and complete recovery were empyema and chronic pulmonary disease on which pneumonic consolidation was superimposed. Among the cases with complications other than empyema it may be stated that when treatment was switched to sulfadiazine no appreciable response was obtained.

Clinical Response in Relation To Dosage. In attempting to estimate the amount of penicillin necessary to suppress the infection, the injections in selected patients were arbitrarily interrupted after the first or second day of treatment. Most of the patients in these groups received 30,000 to 40,000 units per day in divided doses of 10,000 units each. The reaction of the infection to the measured treatment has served as a source of information with regard to the degree and duration of the response in relation to quantity of the drug.

Table II contains data derived from patients in whom injections of penicillin were arbitrarily withheld following either one or two days of therapy. An analysis of the material in Table II reveals the following:

In each of the seven cases in which penicillin therapy was adminis-

TABLE II

COURSE OF PATIENTS IN WHOM ADMINISTRATION OF PENICILLIN WAS INTERRUPTED AFTER ONE OR TWO DAYS OF THERAPY

Patient	*Admin. Day of Disease*	*Pneumonia Type*	*Blood Culture*	*Penicillin—1st Day*		*Penicillin—2nd Day*		*Initial Response*	*Subsequent Course*
				No. of Injections	*Daily Amount*	*No. of Injections*	*Daily Amount*		
J. Z.	3rd	Unclassified	—	3	30,000	—	—	Yes	Rapid Recovery
M. H.	3rd	VII	—	3	30,000	—	—	Yes	Relapse
D. R.	2nd	Unclassified	—	4	40,000	—	—	Yes	Rapid Recovery
V. J.	2nd	XI	—	4	40,000	—	—	Yes	Rapid Recovery
B. M.	3rd	II	—	4	40,000	—	—	Yes	Relapse
F. T.	?	XX	+	5	50,000	—	—	?	Prolonged
J. G.	3rd	VIII	—	7	70,000	—	—	?	Died
L. T.	4th	II	—	4	40,000	3	30,000	Yes	Rapid Recovery
A. K.	3rd	V	—	6	60,000	3	30,000	Yes	Relapse?
J. B.	5th	II	—	4	40,000	4	40,000	Yes	Relapse?
A. L.	3rd	Unclassified	—	4	40,000	3	30,000	Yes	Relapse
E. F.	1st	II	+	4	40,000	5	50,000	Yes	Relapse
M. B.	4th	V	+	4	40,000	5	25,000	Yes	Empyema
O. B.	?	I	+	3	30,000	3	30,000	?	Died

tered on the first day and then interrupted, there was a significant drop in temperature to below 101° in 16 to 24 hours but permanent cure was not uniformly effected.

In each of the two patients in the one day group with bacteriemia a second blood culture taken on the second hospital day was sterile.

With the exception of the patient who died 36 hours after admission, symptomatic improvement accompanied the early fall in temperature.

Complete cure followed a single series of injections given for one day in three cases. However, it should be noted that the pneumococci isolated from their sputum belonged to serological types not usually associated with severe pneumonia. Consequently, the mildness of the pneumonia may have promoted the striking response even though the patients were treated early in the disease, i.e., 3rd, 2nd and 2nd days respectively.

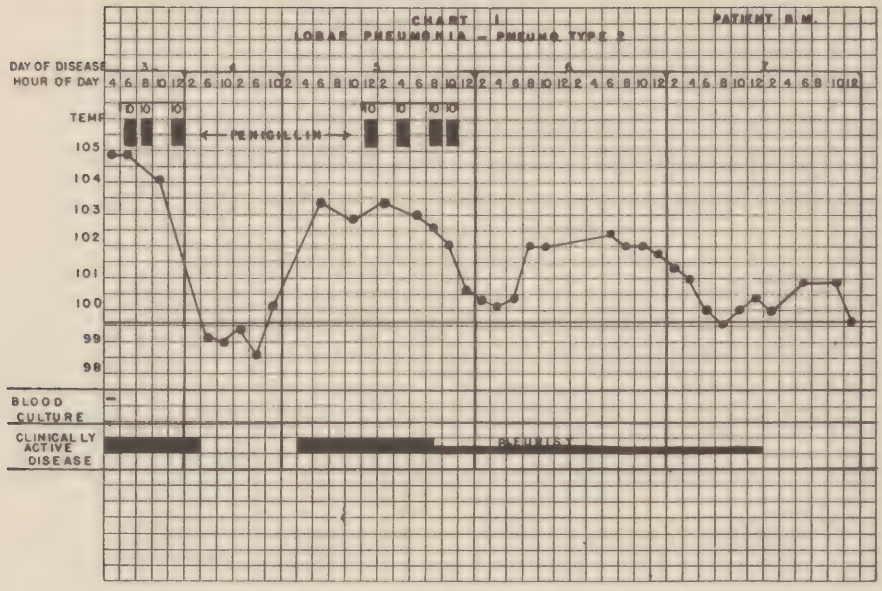
In the three remaining cases who recovered and in whom treatment was withheld after the first day, a relapse of the infection occurred. Recovery, however, promptly followed the reinstitution of treatment.

In the patients who were treated on *two consecutive days* before withholding therapy, with the exception of the fatal case, improvement followed the first day of therapy. Consequently, the second series of injections was given after improvement had begun. In each instance of bacteriemia in this group, the blood culture taken on the second day was sterile and remained so.

As to the final outcome following two days of treatment one of the patients made a rapid and permanent recovery, whereas, among the remaining cases in this group, two had transient rises of fever to 101° to 102° appearing 48 hours after the last injection and spontaneously receding within two days, and the other two had definite relapses.

From a consideration of the findings given in Table II it appears that penicillin in the dosages employed evoked rapid early improvement indicating the high degree of sensitivity of the infecting pneumococci to penicillin. It is also evident that relapse was liable to occur if treatment was not extended longer than two days.

From the standpoint of chemotherapy the importance of the development of type specific immunity in promoting permanent recovery from pneumococcus infections has been illustrated both experimentally and clinically in relation to sulfonamide therapy. MacLeod[10] demon-

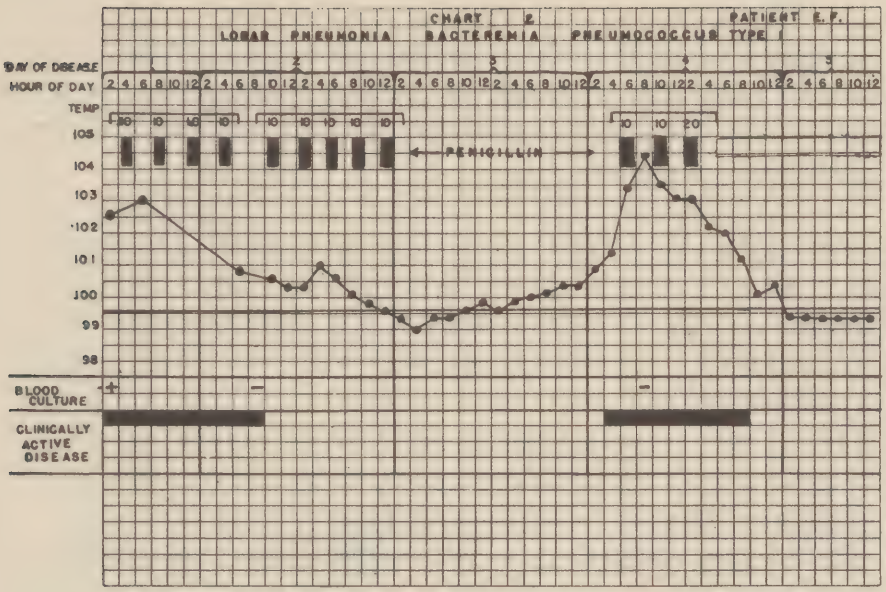


strated in mice that the suppression of pneumococcal infection by sulfapyridine was made permanent by the appearance of type specific immunity. In pneumonia the observation has been repeatedly made that patients treated early (first to third day) with appropriate sulfonamides are liable to relapse if treatment is stopped in one or two days.

In comparing the experience with sulfonamides with that encountered with penicillin it seems probable that the continuance of treatment as determined by the day of disease is of equal importance with either of the drugs.

For purposes of demonstrating graphically the quantitative relationships between dosage and its effect on the infection with particular reference to the duration of the remission after premature withdrawal of treatment, the details of the courses of two patients are given in Charts 1 and 2.

Chart 1 is that of a patient with pneumonia due to pneumococcus, Type II, who was admitted on the 3rd day of disease. Following the details of the temperature chart it may be seen that the last dose of penicillin on the first day was given at approximately 12 midnight and that the temperature became normal between 12 and 6 the following morning—12 hours after beginning therapy. That the therapeutic effect



was not solely antipyretic is evidenced by the marked alleviation of symptoms during the afebrile period. The patient became worse at about 4 o'clock on the morning of the 3rd hospital day, approximately 28 hours after the last injection. In view of the fact that measurable amounts of penicillin have been found by Rammelkamp and Keefer[11] to disappear from the blood within 3 hours after injection, the disease in this patient was restrained for approximately 25 hours after the blood level of penicillin was presumably zero.

The second series of injections of penicillin given on the 3rd hospital day was also followed by a definite response. A dry pleurisy persisted for two additional days but complete recovery was not further delayed.

Chart 2 is that of a patient whose course was particularly instructive. He was admitted eight hours after a chill which initiated the attack of pneumonia. Injections of penicillin were begun promptly. His blood culture was positive for pneumococcus, Type 1. His course illustrates the importance of taking into account the day of disease on which therapy is begun in determining the duration of therapy. In this patient two series of injections on two consecutive days were given before withdrawal of treatment. His response to the first four injections of the first

day occurred, as indicated in Chart 2, within 16 hours. A second blood culture taken five hours after the last previous injection of penicillin was sterile. The initial early improvement was maintained for approximately 28 hours after treatment was stopped. A relapse then occurred abruptly, although a blood culture taken at the height of the febrile exacerbation was negative.

Penicillin therapy was again instituted on the fourth day. Subsequently in this case sulfadiazine was given as supplementary treatment during the latter part of the fourth day because the patient was encountered early in the trials of penicillin before its efficiency for pneumonia had been well established. Permanent recovery occurred on the 6th hospital day.

The course of the two patients just described, in addition to illustrating the rate of response, also demonstrates the duration of the period of remission after premature interruption of treatment.

Results comparable to those just described have been observed in other patients who were followed in a similar manner. In summary, they indicate that, in the average uncomplicated case of pneumonia, the administration of 30,000 to 40,000 units per day in divided doses initiates improvement. Furthermore, the remission evoked by the therapy endured for approximately 20 to 28 hours before the effect of the penicillin was lost.

These findings have afforded useful information in formulating a complete course of treatment with respect to quantity and spacing of dosage.

Additional data of a similar character have been derived from an analysis of the course of the patients with bacteriemia in relation to the injections of penicillin which they received.

Effect of Penicillin on Bacteriemia. Fourteen of the patients had bacteriemia on admission. In each instance following penicillin therapy the second blood culture was sterile. In seven of the patients the time relationships between the second blood culture and the last previous dose of penicillin is sufficiently definite to offer information concerning the duration of the sterilizing effect. The findings are contained in Table III.

The quantitative range of dosage during the first 24 hours in this particular group of bacteriemic cases was from 30,000 to 105,000 units. The differences in amounts of penicillin that were administered oc-

TABLE III

AMOUNT OF PENICILLIN EFFECTIVE IN ALTERING BACTERIEMIA*

Pneumo Type (Patient)	*1st Blood Culture*	*Amt. of Penicillin before 2nd Bl. Culture Units*	*Route of Administration*	*2nd** Blood Culture*	*Interval between previous dose of Penicillin and 2nd Blood Culture*
I (J. S.)	+	105,000	75,000 Intravenous 30,000 Intramuscular	—	3 hrs.
I (J. St.)	+	90,000	25,000 Intravenous 65,000 Intramuscular	—	5 hrs.
II (M. L.)	+	60,000	Intravenous	—	6 hrs.
II (E. F.)	+	40,000	Intravenous	—	9 hrs.
III (B. R.)	+	40,000	Intravenous	—	5 hrs.
VIII (J. G.)	+	60,000	Intravenous	—	16 hrs.
I (O. B.)	+	30,000	Intravenous	—	10 hrs.

*In the six other cases which had bacteriemia on admission the 2nd blood culture was sterile, but it was not taken until the 2nd or 3rd day of hospitalization.

**In each instance the 2nd blood culture was taken approximately 20-24 hours after the 1st.

curred for the most part in connection with explorations of dosage which was altered as experience developed. That the blood stream was cleared in each instance is striking evidence of the potency of penicillin in its antipneumococcal action.

It is of further interest to note from Table III the time of the last previous dose of penicillin in relation to the time of taking blood for the second culture. From the figures in the table it may be seen that intervals of from 3 to 16 hours elapsed but that the bacteriemia did not return. By the method which they employed, Rammelkamp and Keefer[11] found that penicillin was detectable in the blood for 30 to 210 minutes after intravenous injection, the time varying according to the dosage of the drug. On the basis of the figures of these authors, it may be estimated that, in the bacteriemic patients described in Table III, the initial clearing of the blood was maintained in different patients for varying periods of time up to at least 13 hours after circulating penicillin was presumably no longer detectable. Consequently, the damaging effect of penicillin on the invasive pneumococci appears to have restrained their regrowth for an appreciable period after the blood level ceased to be measurable.

Each of the patients of Table III received penicillin intravenously. Whether the rapidity and persistence of the clearing of the blood of pneumococci is best accomplished by intravenous medication has not been determined since comparable studies have not been made following intramuscular injections. The findings in the bacteriemic cases when combined with the results illustrated in the previous Tables and Charts suggest that the maintenance of a definite level of penicillin continuously may not be a necessary detail of satisfactory treatment.

Discussion of Factors Involved in the Application of Penicillin to the Treatment of Pneumonia

Duration of Treatment. On the basis of the experience described in this article it seems apparent that in order to avoid relapses, treatment should be extended over three or four days or for longer periods under special conditions. As stated earlier the duration of treatment is influenced by the day of the disease on which it is started since a remission effected early in the infection (first to third day) may not be maintained unless treatment is continued until the elements of immunity or other factors in the evolution of the disease become operative.

With regard to continued repetitions of injections the data have indicated that when an interval of 12 to 16 hours was permitted to elapse between daily treatments the results were as satisfactory as those obtained by maintaining therapy throughout 24 hours. The special studies demonstrate that the arrest of the infection caused by penicillin was continued beyond the period during which penicillin would be expected to be detectable in the circulating blood.

The reports of Florey and associates[1] and of Rammelkamp and Keefer[11] have described the rapid excretion of penicillin in the urine and also the distribution of the drug in normal body fluids following parenteral injection. However, the extent to which penicillin penetrates into inflamed areas, or the concentration or the persistence of the product in an active state in the extravascular sites of the infection within tissues has not been determined. Whether or not alterations in permeability and diffusion which membranes undergo as a result of inflammation affect the dissemination of penicillin has not been determined.

In interpreting the protracted effect by which the abatement of the infection persisted after the disappearance of circulating penicillin, it seems possible that the result may be dependent upon the retention of penicillin at the local site of the infection for a longer period of time than in the circulating blood, or that the damage inflicted by temporary contact between penicillin and pneumococci is sufficiently severe to delay the further multiplication of organisms.

On the basis of the response of patients, therefore, four injections daily at three hour intervals on three to four successive days has proved satisfactory.

Route of Injection. For the cases of relatively moderate severity, the intramuscular route of injection has been found to be efficacious. However, in patients appearing seriously ill or in those with bacteriemia, the results following intravenous therapy as measured by clinical improvement and disappearance of bacteriemia (Table III) indicate the effectiveness of the intravenous route, which may be preferable for the first few injections.

Amounts per Dose. 10,000 units have been the routine amount employed for intramuscular injection. 10,000 or 25,000 units have been given in intravenous injections, depending on the severity of the case.

Suggested Plan of Treatment. Consolidating the findings that have

been discussed above, the following procedure is tentatively outlined.

Cases of Moderate Severity: 10,000 units of penicillin given intramuscularly every three hours for four doses on each of three and possibly four successive days.

Seriously Ill Cases: 25,000 units given intravenously every three hours for the first two doses of the first day, followed by 10,000 units intramuscularly at three hour intervals for the second two doses of the first day. Subsequent treatment of the second, third, and fourth day to follow plan outlined for cases of moderate severity, i.e., four doses of 10,000 units every three hours for each day.

It is obvious that variations in the clinical course of individual cases may require special alterations in treatment. It should also be emphasized that the above suggestions are not presented as established recommendations but that they represent a current appraisal based on the objective data contained in this report. In view of the low toxicity of penicillin, more extensive therapy than that oulined may be employed without the hazards of serious reactions. However, this study has been directed toward an attempt to define quantitatively the relation of clinical response to therapeutic dosage.

Comparative Value of Penicillin and Sulfadiazine in Pneumonia. Our experience indicates that the therapeutic value of penicillin in pneumonia is at least equal to that of sulfadiazine, and, in addition, there are certain well defined conditions that make the use of penicillin particularly advantageous. They may be summarized as follows:

1. The fact that, up to the present time, no significant toxic manifestations have been noted in association with the administration of penicillin is of special interest. A few cases of urticaria have been described[3] (none in the present series) but the evidence is inconclusive that the eruptions were based on the development of sensitivity. It is, furthermore, uncertain whether such reactions were caused by penicillin or by some contaminating ingredient present in the preparations.

2. Penicillin is particularly serviceable when pre-existing sensitivity to the sulfonamide drugs contraindicates their use, or when sulfonamide toxicity develops during treatment before the infection has been completely overcome.

3. Penicillin has been shown experimentally to be highly effective against sulfonamide-fast pneumococci.[9, 12, 13] In the second part of this article which deals with the local use of penicillin in the treatment of

empyema, the value of penicillin in patients suffering from infections caused by sulfonamide-resistant pneumococci will be described.

It is also of interest to record briefly the favorable response to penicillin of two patients with lobar pneumonia and bacteriemia due to pneumococci refractory to sulfadiazine.

One of the patients in the present series was admitted to the hospital on the seventh day of pneumonia after having received sulfadiazine continuously from the beginning of his illness but without improvement. On admission, in addition to lobar consolidation, he also had bacteriemia due to pneumococcus, Type VII, and a blood level of sulfadiazine of 6.6 mgms. per cent which remained from the pre-admission treatment. By laboratory tests the strain derived from the blood culture proved to be sulfonamide-fast.

Under penicillin therapy the blood culture became sterile within 24 hours and the patient recovered uneventfully in spite of the fact that he also had lymphatic leukemia.

A second instance of infection with a sulfonamide-resistant strain of pneumococcus successfully treated with penicillin was that of a 63-year-old female* who had had pneumonia and an intermittent bacteriemia due to pneumococcus, Type VIII, for approximately 4 weeks before penicillin therapy was instituted. Early in her disease she also developed empyema which was treated surgically by rib resection and drained satisfactorily. She had received sulfadiazine continuously for 4 weeks without permanently altering the bacteriemia. She had also received Type VIII antipneumococcus serum with only temporary improvement. There were no definite signs of endocarditis. On the day following the first injection of penicillin her blood became sterile and remained so. The pneumonia subsided.

In laboratory tests the pneumococci from both the blood culture and the empyemal pus were found resistant to sulfadiazine.

4. Although as yet unsubstantiated by objective data, it seems likely that penicillin sterilizes the blood stream in cases of bacteriemia and suppresses the active infection at a more rapid rate than does sulfadiazine. Although in many instances this difference may not be of special significance, nevertheless in cases of unusually severe infection, the speed of effect may be particularly desirable.

* This case was under the care of Dr. Robert C. Schleussner at the Lenox Hill Hospital and is reported with his permission.

Even though the use of penicillin has the definite advantages just mentioned, the extent to which its widespread use in large numbers of cases of pneumonia would markedly alter mortality statistics is not clear. Analyses of causes of death in cases of pneumonia treated with the sulfonamide drugs[14] have brought out the fact that the majority of the fatalities are due to a variety of complicating circumstances that would not in themselves be overcome even by a more potent anti-pneumococcal drug.

II. The Treatment of Pneumococcal Empyema by the Intrapleural Injection of Penicillin

This study of pneumococcal empyema has been directed toward determining the possible usefulness of chemotherapeutic agents introduced locally as a medical method of treatment which might obviate surgical intervention. In spite of the fact that there seems to have been a decrease in the incidence of empyema caused by pneumococci since the introduction of chemotherapy for pneumonia, the administration of the sulfonamide drugs either by mouth or intravenously has not proved satisfactory in the treatment of empyema after the complication has developed.

At the beginning of the present inquiry observations were made on the course of empyema following the intrapleural injection of sulfadiazine. As a curative measure the initial attempts were unsatisfactory since the pneumococci causing the pleural infections were found to retain viability in the presence of large amounts of the drug and the patient's illness remained unchanged. Consequently, penicillin was employed for local injection.

Up to the present time eight patients with pneumococcal empyema have been treated by the introduction of solutions of penicillin into the infected pleural space. The empyemata, with one possible exception, deevloped as a complication of lobar pneumonia.

Although the details of this report deal with the efficacy of penicillin introduced locally into the empyemal cavities, before proceeding with a description of the methods and results, it is of interest to record briefly some of the observations which were made in connection with local sulfonamide therapy.

The findings are illustrated by the course of one of the patients who was first treated with sulfadiazine and later with penicillin injected

intrapleurally (See Chart 3). After the introduction of sulfadiazine into the empyemal cavity of this patient the sulfonamide content of the exudate reached 415 mgms. per cent. However, on examination of the exudate, pneumococci were seen in direct smears and were viable on culture.

In seeking an explanation for the inactivity of the drug against the organisms as exemplified in the case just mentioned, tests were made for the presence of sulfonamide inhibitors in samples of empyemal exudate obtained from this and other patients. Experiments were also carried out to determine the degree of sulfonamide fastness possessed by several strains of pneumococci derived from empyemal pus.

The results may be briefly summarized as follows:

1. Estimation of the presence of sulfonamide inhibiting substances in pneumococcal pus from cases of empyema.

Five different speciments from four different patients were tested. The method described by MacLeod[15] was employed using a strain of B. coli which was cultivated in an inhibitor-free medium in the presence of varying quantities of sulfadiazine. Exudate was then added and its effect on growth observed. The results obtained in each of the tests failed to reveal the inactivation of sulfadiazine by any of the specimens.

2. Tests for sulfonamide-fastness of empyemal strains of pneumococcus.

Six strains from patients with empyema have been tested by *in vivo* methods, which consisted of infecting mice intraperitoneally and treating them with sulfadiazine, *per os*, twice daily for four days. Five of the strains came from the pleural exudate of patients who were treated at the onset of the pneumonia with sulfadiazine. With each of these strains some degree of drug resistance was evident in that an amount of sulfadiazine sufficient to cure mice infected with laboratory strains of pneumococci was incapable of preventing death in mice infected with empyemal strains.

The sixth strain, however, derived from a patient treated from the beginning with penicillin alone had no degree of drug fastness either to sulfadiazine or penicillin.

Although the findings just outlined are too limited to warrant final conclusions, they suggest that, in cases of pneumonia which develop empyema while receiving sulfonamide drugs, the strain derived from

the pleural exudate may exhibit sulfonamide-resistance. On the other hand, if no sulfonamide therapy has been administered, the empyemal strain may be found to be drug susceptible.

That penicillin warranted trial in this type of infection is indicated by the fact that its antibacterial action against pneumococci is equally potent irrespective of the presence or absence of sulfonamide-fast qualities.[9, 12, 13]

In attempting to develop an effective but uncomplicated method by which penicillin may be utilized locally in pneumococcal empyema, the patients receiving treatment have been studied by correlating their clinical course with the results of laboratory examinations of specimens of pleural exudate derived from the treated area.

The findings have been used as an indication of the degree of effectiveness of varying dosages of penicillin and also as a guide in determining the extent to which repeated injections were necessary.

Material and Methods

In pursuing the studies, samples of pleural effusion were obtained by bedside aspiration at frequent intervals and examined for the presence of viable pneumococci. When pus suspected of containing penicillin was cultured, the specimen was first centrifuged and washed with physiological salt solution in order to avoid transferring a portion of the antibacterial agent contained in the exudate to the broth used for culture media. It may be noted, however, that in comparable tests using 0.1 cc. of specially prepared exudate added to 5 cc. of broth, the preliminary washing did not yield results different from that obtained by adding the same amount of pus directly to the culture media. It seems unlikely that the special technique is necessary as a routine procedure in determining the presence or absence of viable organisms.

In some instances, tests for the presence of penicillin in the exudate were made in order to estimate the duration of its activity following instillation. The method most frequently employed consisted of determining the capacity of the supernatant fluid of centrifuged specimens of effusion to protect mice against infection with pneumococci heterologous in type to that derived from the patient. By this procedure, active penicillin was detected in the exudate for as long as 48 hours after injection in four patients and 72 hours in another patient but was not demonstrable in speciments obtained on the 5th or 6th day following

treatment. As will be discussed later, the duration of sterility has served as a supplementary guide in establishing the quantity and frequency of injections that comprised effective therapy.

Concentration of Penicillin in Solution Used for Injection. Solutions were most commonly made up in a concentration of 1000 units of penicillin in 1 to 1.5 cc. of physiological salt solution. The quantity of solution injected was never in excess of the amount of exudate removed. However, since the largest single dose injected intrapleurally was 40,000 units in 50 cc. and since the amount of exudate aspirated was usually more than 50 cc., the necessity of using a more concentrated solution in order to introduce the desired number of units did not frequently occur. In view of the moderate irritating effect of penicillin on the serous surface of the pleura as indicated in Table IV, the concentration may, under some circumstances, require consideration.

Clinical Course and Laboratory Findings of the Patients

The results derived from the study are given in the form of a brief resume of the course of each patient. Charts of four of the patients are included. X-ray photographs, taken before treatment was begun and after recovery, of 6 patients are appended at the end of this article.

Case 1. Patient A.Mc., male, white, age 57 years.

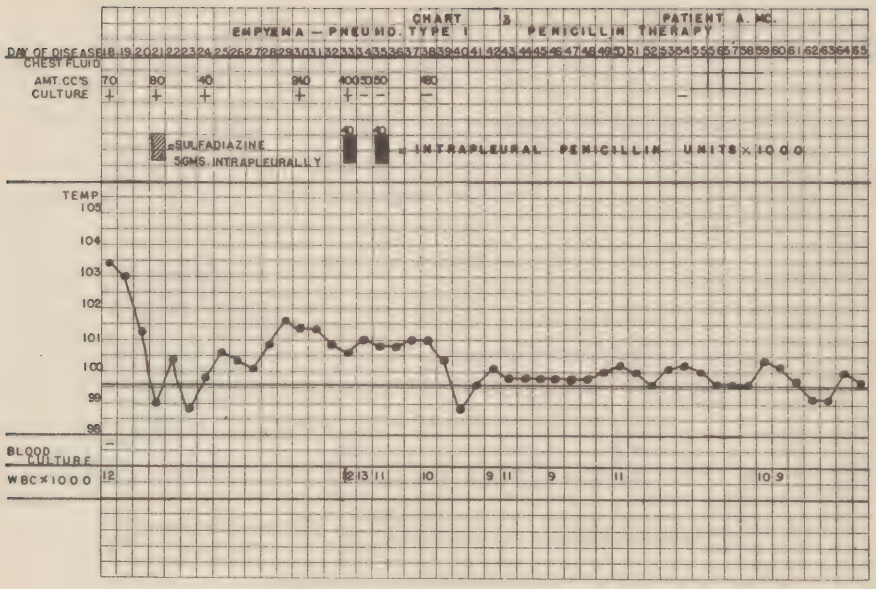
Diagnosis: Lobar pneumonia, bacteriemia, empyema, Pneumococcus, Type I.

The patient was admitted to our wards on the 21st day of illness. In the early stages of pneumonia he had been treated with sulfadiazine. The blood culture became sterile and pneumonia subsided following sulfadiazine therapy but signs of pleural effusion developed. On three separate occasions during the first two weeks of the patient's illness purulent material containing Type I pneumococci was obtained by thoracentesis. One week after the last of the preceding aspirations the patient came under our observation.

The patient's course is illustrated in Chart 3.

From Chart 3 it may be seen that the local treatment of empyema first consisted of 5 gms. of sulfadiazine injected intrapleurally. As mentioned earlier the failure of sulfadiazine to sterilize the cavity was accounted for by the drug-fastness of the infecting strain.

At the time of the first injection of penicillin 400 cc. of thick puru-



lent exudate containing many pneumococci were withdrawn before introducing 40,000 units contained in 50 cc. of isotonic salt solution.

In a sample of exudate obtained on the day following the first treatment, misshapen gram positive forms were seen in direct smears, but cultures were sterile. In a specimen obtained 48 hours after treatment, no gram positive forms were seen; cultures were sterile. At the time of the latter thoracentesis a second dose was administered consisting of 40,000 units. Although two subsequent samples of pleural exudate were obtained 3 and 17 days respectively after the second treatment, pneumococci could not be seen in or cultivated from either specimen.

From a clinical standpoint the patient's general condition was satisfactory throughout the period of treatment although convalescence was somewhat protracted. A low grade fever (100°F) continued for 30 days. During this period discomfort in his chest was present but was not severe. There were some night sweats and a moderate leukocytosis was maintained. However, when the temperature became normal, the evidences of infection disappeared.

Repeated x-ray examinations of the chest reevaled the gradual clearing of a homogenous shadow over the affected area. At a final x-ray examination made two months after discharge from the hospital, the

X-RAY PHOTOGRAPHS OF CASE 1.

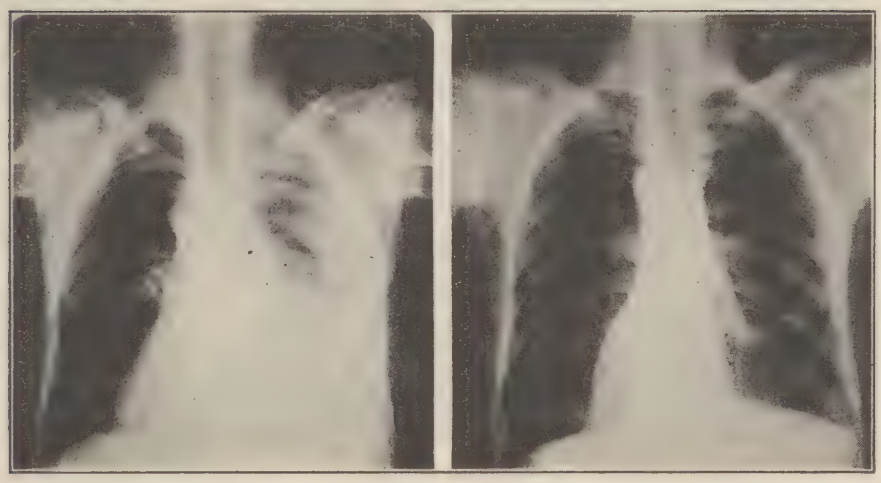


Fig. 1 Before penicillin therapy. Fig. 2 Two months after leaving hospital.

only evidence of abnormality consisted of a small localized band of increased density in the left lateral costophrenic angle.

Resume: Total Number of Intrapleural Injections of Penicillin: Two.

Amount per Dose: 40,000 units.

Total Amount: 80,000 units.

Result: Pleural exudate sterile 24 hours after first treatment. No relapses. Recovery complete with limited residual pleural thickening.

Duration of Hospitalization After Beginning of Treatment: 42 days.

Case 2. Patient E.M., male, colored, age 35 years.

Diagnosis: Lobar pneumonia, bacteriemia, empyema (multiple foci). Pneumococcus, Type VIII.

The patient was treated for the first 10 days with sulfadiazine by mouth. Blood culture became sterile but high fever persisted. Empyema was detected on 6th hospital day. Sulfonamide-fastness of empyemal strain was demonstrated by laboratory tests.

The first intrapleural injection of penicillin (20,000 units) was given on the 10th hospital day. Three additional doses (15,000, 20,000, and 25,000 units respectively) were given into the same site as that of the first injection. The latter treatments were administered on the 2nd,

X-RAY PHOTOGRAPHS OF CASE 2.

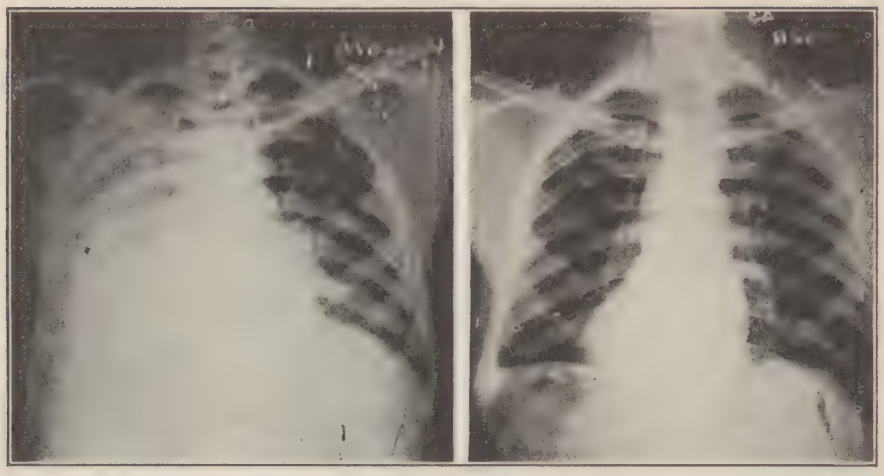


Fig. 3 Before penicillin therapy. Fig. 4 Four months after leaving hospital.

4th, and 7th day after the initial instillation. Five samples of exudate were taken from the area subjected to repeated treatments between the 1st and 15th day after beginning injections and, in each instance, cultures were sterile.

In spite of the disappearance of pneumococci from the site of infection receiving the repeated injections, the patient continued to be acutely ill. By additional explorations, a second pocket of empyema was found, the exudate from which contained Type VIII pneumococci. Before penicillin therapy was instituted into the second area, the patient began to cough up large quantities of purulent material. The course was interpreted as indicating that the second pocket was being drained through a bronchopleural opening. After 2 weeks the sputum became scanty and ceased to be purulent. The patient was improved but not afebrile.

Subsequently his temperature rose to 104.5°. A third pocketed area was discovered distant from the other two. No viable pneumococci were recovered from the purulent fluid of this area but a precipitin test performed by mixing the specimen of exudate with Type VIII antipneumococcus serum was strongly positive.

Into the third area 20,000 units of penicillin were injected. Within 48 hours the patient's temperature was normal and his convalescence

to recovery was rapid. X-ray photographs are appended. The last picture was taken four months after discharge from hospital.

Total Number of Intrapleural Injections of Penicillin: Four into the first focus, one into the third focus.

Amount per Dose: 20,000—15,000—20,000—25,000 units into the first pocket; 20,000 units into the third pocket.

Total Amount: 100,000 units.

Result: Pleural exudate of first pocket sterile 24 hours after first treatment. No recurrence of infection in first area but additional pockets were present. Final recovery was complete with limited residual pleural thickening.

Duration of Hospitalization: 62 days after beginning treatment, 15 days after treatment of last localized area of infection.

Case 3. Patient M.B., white, male, age 33 years.

Diagnosis: Lobar Pneumonia, Empyema. Pneumococcus, Type V.

The patient was treated for the first five days with sulfadiazine by mouth. Empyema was detected on 2nd hospital day. Local penicillin therapy was instituted on the 3rd hospital day by injecting 40,000 units intrapleurally. No additional treatments were given.

The pleural exudate obtained from each of two pre-treatment taps contained Type V pneumococci. From five subsequent aspirations performed two, six, eight and fifteen days after instillation of penicillin, 200-300 cc. of cloudy material were obtained. No pneumococci were present.

His general condition progressed satisfactorily except for low grade fever which continued for 16 days, together with a moderate leukocytosis, and some night sweats. It is interesting to note that in spite of the inability to demonstrate bacteriologically active infection, the exudate in the pleural cavity continued to accumulate for approximately two weeks before finally disappearing.

Resume: Total number of Intrapleural Injections of Penicillin: One.

Total Amount: 40,000 units.

Result: Pleural exudate sterile 48 hours after local treatment. No relapses. Clinically recovery was complete, but patient was not under observation for a sufficient length of time to observe the final degree of clearing of x-ray shadow.

Duration of Hospitalization after Beginning Treatment: 25 days.

TABLE IV

IRRITATING EFFECT OF PENICILLIN INJECTED INTRAPLEURALLY

Case No.	*Diagnosis*	*Pleural Fluid W. B. C.*	*Penicillin Units*	*1st Day*			*2nd Day*			*4th Day*		*6th Day*	
				Cells	*Fever*	*Pain*	*Cells*	*Fever*	*Pain*	*Cells*	*Fever*	*Cells*	*Fever*
1	TBC	590	40,000	Not done			1820			560			
2	Cardiac	255	12,500	64,200	+	+	36,800	+	—	3200	—	310	—
3	Cardiac	320	10,000	17,500	+	+	13,500	+	—	2920	—	810	—
4	Cardiac	620	10,000	14,500	+	+	8900	—	—	2750	—	1680	—
5	Cardiac	180	5,000	15,500	+	+	2190	—	—		—	1000	—
6	Pneu.	210	5,000	2975	+	+			—	1225	+		
7	Alc. Cirv.	770	5,000		—	—	1150	—	—			250	—
8	Cardiac	1830	5,000	5,500	—	—							
9	Cardiac Same as 2	340	Control	520	—	—		—		540	—		

The special features of the cases so far described consisted of: 1. The rapidity of sterilization of the empyemal cavity following injection of penicillin; 2. The persistence or probable reaccumulation of purulent exudate without demonstrable pneumococci; 3. The somewhat prolonged convalescence with low grade fever; 4. The ultimate recovery.

In considering an explanation of the course, which was characterized in each of the patients by rapid bacteriological "cure" but somewhat delayed clinical resolution, the possibilities which suggested themselves were that a small focus of undetected living organisms remained under the fibrin coating of the pleura even though aspirated material was sterile, or that the decomposition of the sterile pus produced toxic substances acting as irritants, or that the penicillin was itself irritating locally.

The latter possibility lent itself readily to testing. Accordingly, solutions containing from 5,000 to 40,000 units were injected intrapleurally into eight patients who suffered from hydrothorax due to various causes. The penicillin was introduced after removal of most of the transudate. Subsequent samples of the effusion were obtained on each of the following four to six days and the number of cells per cmm. was determined. The presence or absence of fever or thoracic pain was also noted. The results are contained in Table IV.

In each instance there was a definite but variable rise in the number of cells which was greatest the day after injection and gradually decreased during the ensuing days until a number slightly above the preinjection level was reached on the 4th to 6th day. Slight fever (100-101°) and some thoracic pain were present on the day following injection but disappeared within 48 hours.

In view of the evidence of a moderate irritating action of penicillin on the pleural surfaces, the next two patients received smaller doses of penicillin than those employed in the cases already described. The attempt was made to employ a sufficient number of units to obtain the necessary antibacterial effect but to minimize the untoward local reaction. That the dosage employed for that purpose was insufficient is evident from the relapses which occurred in the next two patients.

Case 4. Patient M.L., white, female, age 42 years.

Diagnosis: Lobar pneumonia, Bacteriemia, Empyema. Pneumococcus, Type V.

X-RAY PHOTOGRAPHS OF CASE 4.

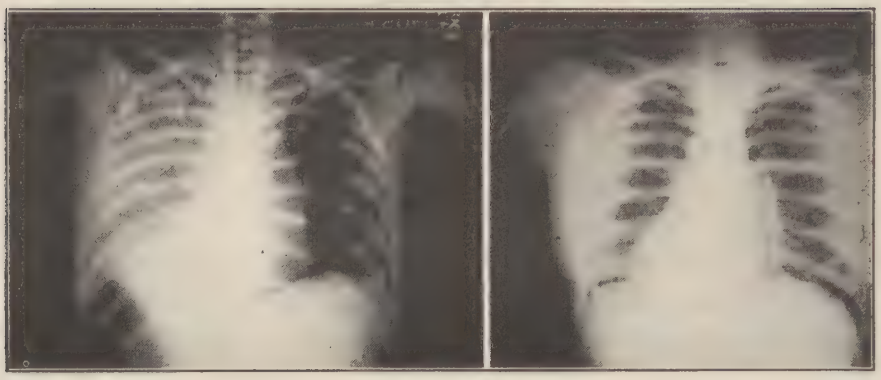


Fig. 5 Before penicillin therapy.

Fig. 6 Two months after leaving hospital.

On admission, treatment for the first three days consisted of penicillin given intravenously. A total of 130,000 units was administered. The bacteriemia cleared within 24 hours. Empyema was demonstrated on the 4th hospital day.

It is interesting to note that penicillin given during the early acute phase of the illness did not in this instance prevent the development of empyema.

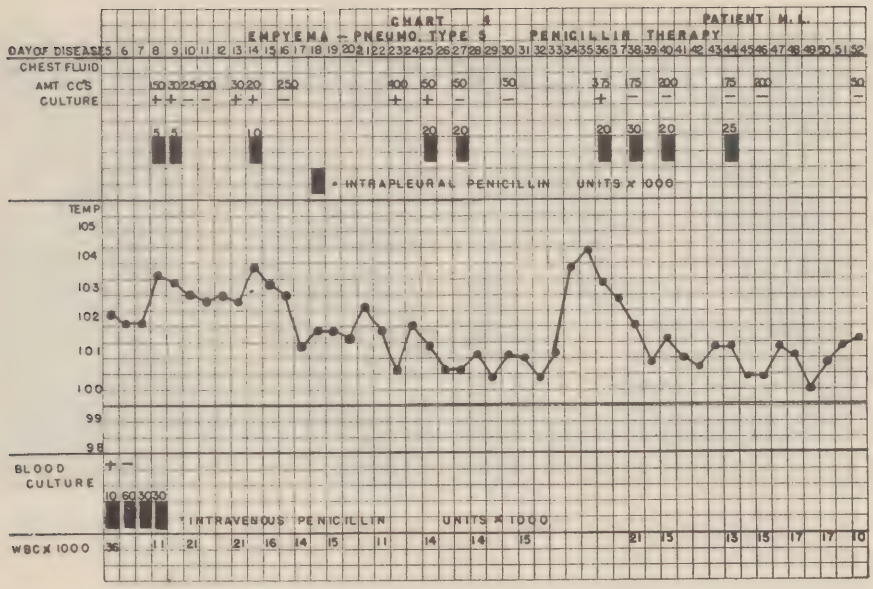
The difficulties in the course of the empyema in Case 4 which were referable to insufficient treatment are illustrated in Chart 4.

From Chart 4 it may be noted that following the injection of 5,000 units, the cavity was not sterilized but that after the second injection of an additional 5,000 units, two aspirations performed 24 and 48 hours later yielded material from which pneumococci were not obtained.

The patient, however, had three subsequent relapses as measured by a return of cultivable pneumococci to the pleural exudate. At each recurrence the dosage of penicillin was gradually increased. The infection was finally overcome by administering four separate doses on alternate days of 20,000-30,000 units.

In spite of her prolonged and irregular course due to inadequate treatment at the beginning, recovery occurred without any greater residue of pleural thickening than that seen in the other cases.

X-ray photographs are appended the last of which was taken two months after discharge from the hospital.



Resume: Total Number of Intrapleural Injections of Penicillin: 9.

Amount per Dose: As indicated in Chart 4 they varied from 5,000 to 30,000 units.

Total Amount: 155,000 units.

Result: Three recurrences of demonstrably viable pneumococci after transient periods of negative cultures. Ultimate recovery was complete with limited pleural thickening.

Duration of Hospitalization after Beginning Treatment: 79 days.

Case 5. Patient M.J., white, male, age 2 years, 3 months, admitted to Pediatric Service of Bellevue Hospital* on 6th day of disease.

Diagnosis: Lobar Pneumonia, Empyema. Pneumococcus, Type XVI.

The patient was treated with sulfathiazole and sulfadiazine for the first 12 days of hospitalization without notable improvement. The first successful thoracentesis yielding pus was performed in the 14th hospital day.

The treatment with penicillin in this patient was started by using small doses as in Case 4. The first injection consisted of 5,000 units.

* The patient's record is presented with the permission of Dr. James Wilson, Director of the Pediatric Service.

X-RAY PHOTOGRAPHS OF CASE 6.

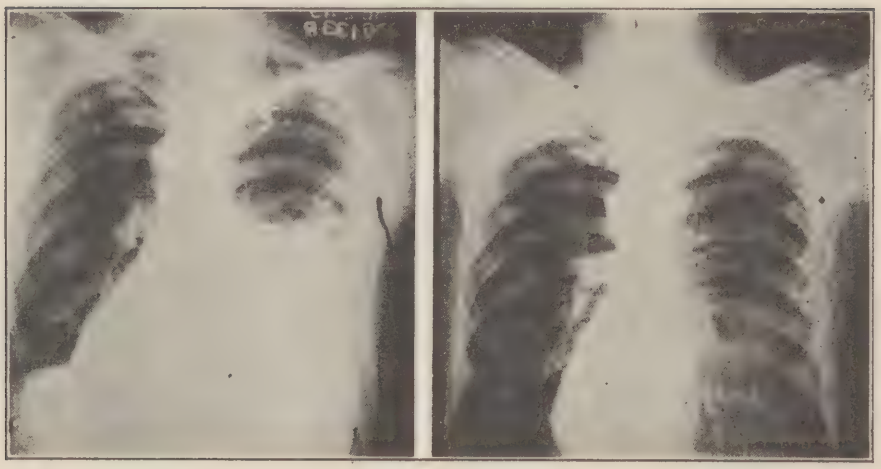


Fig. 7 Before penicillin therapy. Fig. 8 Four months after leaving hospital.

Two aspirations done one and five days after treatment yielded exudates which were sterile on culture. Viable organisms returned, however, within six days. Additional intrapleural doses of 15,000 and 10,000 units were administered which afforded only transient suppression of cultivable organisms.

Following the second relapse surgical drainage was carried out by rib resection. The patient recovered after a prolonged postoperative convalescence.

Resume: Total Number of Intrapleural Injections of Penicillin: 3.

Amount per Dose: 5,000—10,000—15,000 units.

Total Amount: 30,000 units.

Result: Penicillin therapy unsatisfactory due to insufficient dosage. Surgical drainage required. Recovery was complete.

Duration of Hospitalization: 131 days following thoracotomy.

Case 6. Patient, J.D., white, male, age 58 years.

Diagnosis: Lobar Pneumonia, Empyema, Pneumococcus, Type I.

The patient was treated with sulfadiazine by mouth for the first eight days of his illness. Empyema was diagnosed on the sixth hospital day. The empyemal strain was found to possess a definite degree of sulfonamide resistance. Following aspiration of the chest on the eighth

hospital day, 25,000 units of penicillin were instilled into the empyemal pocket.

Both of the pre-treatment specimens of pleural exudate were positive on culture for Type I pneumococci. Material aspirated on the day following treatment was sterile. Cultures of all subsequent samples were also negative.

The total amount of treatment given to the patient consisted of three injections of 25,000 units each injected on alternate days.

His clinical course, similar to that of the other patients who did not suffer relapse, was characterized by gradual improvement, but he maintained a slight fever of 99.5 to 100.5° until the 47th hospital day. The delayed absorption of the thick though sterile exudate was particularly striking.

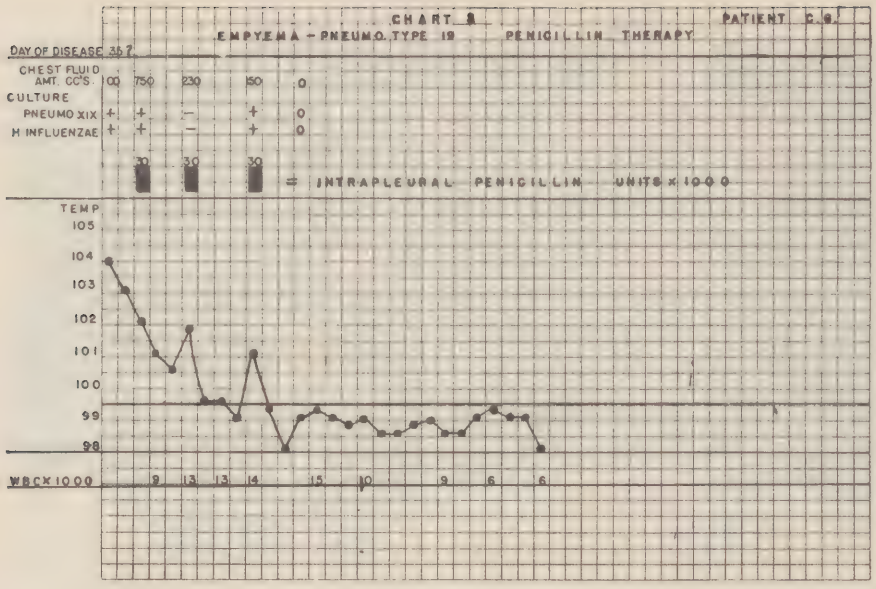
In considering the possibility that the protracted low grade illness might be caused by active undetected infection, intensive therapy was carried out for six days. During the first three days 140,000 units of penicillin were given intravenously and 30,000 units were injected on two occasions intrapleurally. During the remaining three days 20 gms. of sulfadiazine were administered by mouth. No appreciable response occurred.

As an additional measure, when no signs of gradual absorption of the residual exudate could be detected, the site of the pleural pocket was irrigated with physiological salt solution in order to remove as much as possible of the degenerated abacterial pus. Following three irrigations on alternate days the presence of exudate was no longer demonstrable. No effusion reformed and progress to recovery was uneventful.

Resume: Total Number of Intrapleural Injections of Penicillin: 3.
Amount per Dose: 25,000 units.
Total Amount: 75,000 units.

(The amounts given above do not include the late period of additional therapy since the latter treatment did not influence the abacterial pus.)

Result: Pleural exudate sterile 24 hours after first treatment. No relapses. Recovery was complete with residual thickening of pleura.
Duration of Hospitalization after Beginning Treatment: 51 days.



Case 7. Patient C.G., white, female, age 27 years.

Diagnosis: Pneumonia, Pneumopyothorax. Pneumococcus, Type XIX, Hemophilus Influenzae.

The patient had been ill six weeks before admission with a disease which began as an upper respiratory infection. Her local physician had tapped her chest on one occasion and obtained fluid. When her condition remained unchanged she was admitted to the hospital suspected of having tuberculosis. Her course is illustrated in Chart 5.

On admission x-ray examination revealed the presence of both an effusion and air in the right pleural cavity; 100 cc. of thick purulent exudate were removed by thoracentesis. Pneumococcus, Type XIX and Hemophilus influenzae were both seen and cultured from the pus.

Following a second aspiration performed two days later, 30,000 units of penicillin were introduced after removal of 750 cc. of infected exudate.

Cultures of material obtained three days later yielded no growth. The suppression of H. influenzae is of interest since Fleming[4] did not find the strains of H. influenzae which he tested to be susceptible to the antibacterial action of penicillin. It seems likely that the concentration of penicillin introduced into the pleural cavity may have accounted for

X-RAY PHOTOGRAPHS OF CASE 7.

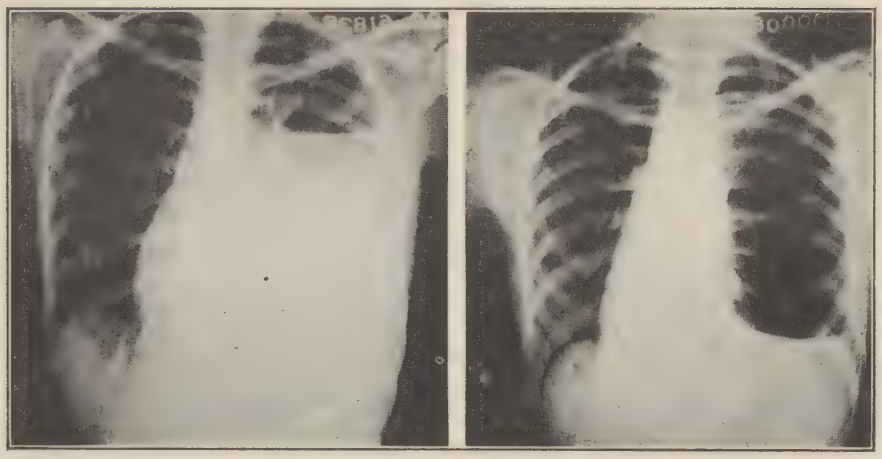


Fig. 9 Before penicillin therapy. Fig. 10 Two months after leaving hospital.

the effect or that the patient's strain was unusually susceptible to penicillin.

Four days after the second intrapleural treatment, pneumococci and H. influenzae were again seen in smears and cultivated from an aspirated sample of exudate. However, after the third instillation of 30,000 units subsequent efforts to obtain fluid were unsuccessful. The patient rapidly improved, her temperature becoming normal 18 days after beginning treatment.

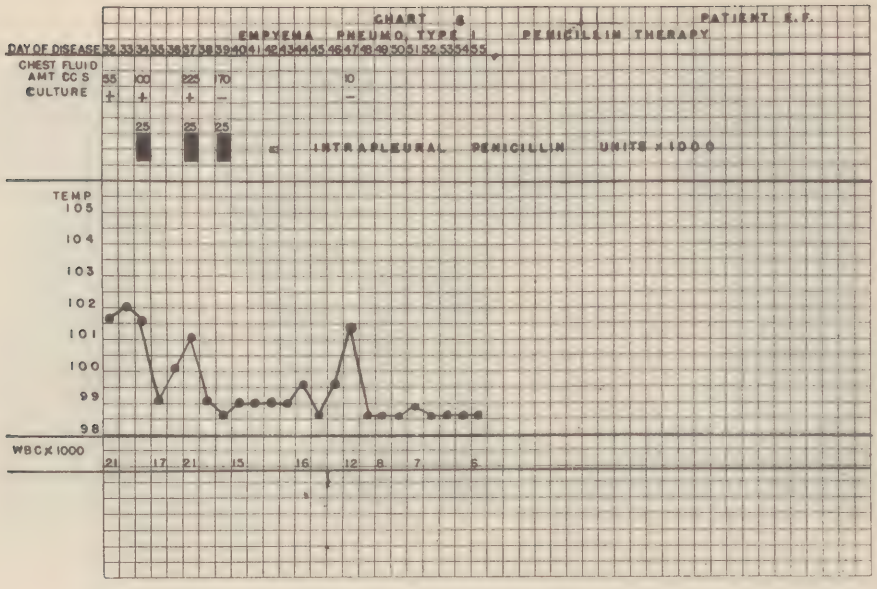
The unusual feature of the course of this patient was the persistence and even increase in the pneumothorax in spite of the rapid disappearance of the pyothorax. Her general clinical improvement paralleled her temperature course as presented in Chart 5. Up to the present time, four months after discharge from the hospital, no signs of effusion have developed in the affected side, but the bronchopleural fistula remains unhealed.

Resume: Total Number of Intrapleural Injections of Penicillin: 3

Amount per Dose: 30,000 units.

Total Amount: 90,000 units.

Result: One bacteriological relapse following second treatment. The pyothorax together with clinical and laboratory signs of infection disappeared but pneumothorax persisted.



Duration of Hospitalization Following Beginning of Treatment: 26 days.

Case 8. Patient E.F.,* colored, female, age 11 years.

Diagnosis: Lobar Pneumonia, Empyema. Pneumococcus, Type I.

The patient, treated on the Pediatric Service, received sulfadiazine for the first few days but continued to be ill. Suggestive signs of pleural effusion developed but pus was not obtained until 25 days after admission. Type I pneumococci were present in the exudate.

The course of the illness is represented in Chart 6.

The patient received 25,000 units of penicillin on three occasions, spaced three and two days apart respectively. Cultures of the exudate were sterile after the second treatment. The clinical improvement was rapid, her temperature becoming normal five days after receiving the initial injection of penicillin.

Resume: Number of Intrapleural Injections of Penicillin: 3.

Amount per Dose: 25,000 units.

Total Amount: 75,000 units.

Result: Pleural exudate sterile five days after beginning treatment. No relapses.

* See Page 156.

X-RAY PHOTOGRAPHS OF CASE 8.

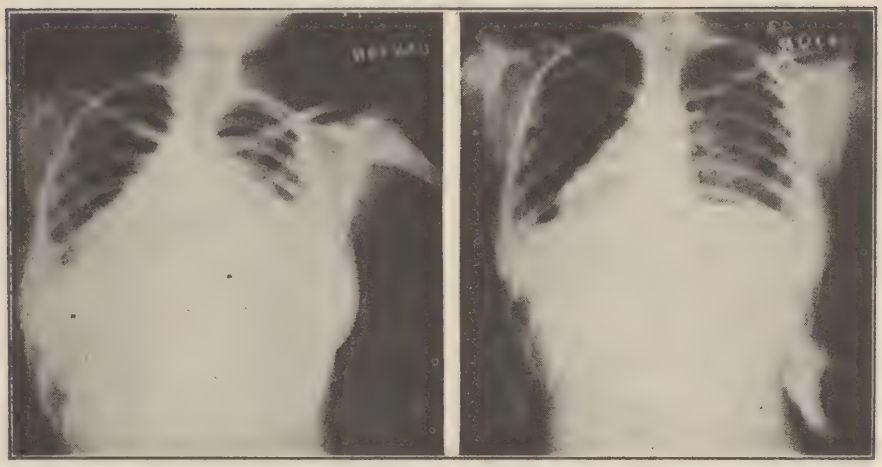


Fig. 11 Before penicillin therapy.

Fig. 12 One week after leaving hospital.

Recovery was complete.

Duration of Hospitalization After Beginning Treatment: 21 days.

Discussion and Outline of Treatment

It is evident from the results which have been described that penicillin injected locally into the pleural cavity is capable under proper circumstances of effecting a cure in pneumococcal empyema without requiring surgical drainage. In developing the most suitable procedure for administering the drug consideration has been given to the therapeutic requirements with respect to amount of penicillin per dose, the frequency with which the injections should be repeated, and the number of repetitions that may be necessary. Although no arbitrary standards may be set at the present time, the favorable results so far obtained constitute a basis for formulating the details of treatment.

Amount of Penicillin, per dose, for Intrapleural Injection. In the two cases which received 5,000 to 10,000 units, pneumococci disappeared temporarily from the pleural exudate as determined by microscopic examination and culture of the specimens but relapses occurred in both instances.

When larger doses ranging from 25,000 to 40,000 units were employed, in only one instance did a relapse occur (Case 7), and even in

that case the infection was subsequently eliminated following one additional dose.

On the basis of present experience, therefore, 30,000 to 40,000 units appears to be an adequate amount per dose.

Frequency of Injections. The preliminary studies mentioned earlier in this article indicated that the activity of penicillin is retained for at least 48 hours to 72 hours after injection into an empyemal pocket. The fibrinous exudate appears to retard absorption but does not destroy the antibacterial quality at a rapid rate.

Furthermore, the tests carried out with repeated samples of exudate have shown that the initial suppression of the organisms that follows treatment is maintained for at least two to three days.

On the basis of these findings, therefore, no demonstrable advantage seems to be gained by performing thoracentesis oftener than every other day.

Number of Repeated Injections. Even though Case 2 recovered following a single injection of 40,000 units, and Case 1 received only two injections of 40,000 units each, treatment in the other patients was extended to at least three separate injections. In view of the fact that the end point of active infection is liable to be obscured by the persistence of low grade fever and the delayed absorption of the exudate even though sterile, the determination of the time at which treatment may be stopped has not been clearly defined. On the basis of practical experience, however, when clinical improvement appears to be progressive and the exudate remains sterile, three separate injections may, in most instances, be sufficient.

Plan of Treatment

Thirty to forty thousand units of penicillin contained in 30 to 50 cc. of isotonic salt solution injected intrapleurally on alternate days for at least three doses.

As a further measure in hastening recovery it is desirable at the time of bedside aspiration to irrigate the cavity with a few hundred cc. of physiological salt solution before introducing the penicillin and to repeat the procedure, if necessary, at intervals of several days after treatment is stopped in order to hasten the removal of the degenerated sterile exudate and minimize the reaccumulation of an effusion.

Summary

I. *Lobar Pneumonia.* Penicillin has been found to be highly effective in the treatment of pneumococcal pneumonia.

Of 46 treated patients, 3 (6.5 per cent) died and 39 recovered in a striking manner indicating the special value of the drug. The response was not clearly defined in 4 patients, one of whom probably had primary atypical pneumonia and the other 3 had unrelated underlying pulmonary diseases which prolonged their illness beyond the usual course of pneumonic resolution.

Bacteriemia, which occurred in 14 of the patients, disappeared in every instance following injections of penicillin.

On the basis of quantitative data presented and discussed in this article, a tentative regime for the treatment of pneumonia with penicillin is outlined.

Factors relating to the relative values of penicillin and sulfadiazine in the treatment of pneumonia are discussed.

II. *Pneumococcal Empyema.* Eight patients with pneumococcal empyema have been treated by intrapleural injections of penicillin.

In seven, the infection was eliminated by the local therapy without requiring surgical drainage. Six of them recovered completely with only a restricted area of pleural thickening remaining as a permanent alteration.

In one patient, who had pyopneumothorax on admission, the pyothorax cleared up satisfactorily but the pneumothorax arising from a bronchopleural fistula which was present before treatment was begun, has persisted.

In another patient, who was insufficiently treated at the beginning with penicillin, relapse occurred and surgical drainage was instituted.

Following discharge from the hospital, the patients have returned for reëxamination at varying periods, after one week for one patient, and from 4 to 6 months for the others. With the exception of the case with pneumothorax, the others have remained well and free of symptoms.

Strains of pneumococci derived from the empyemal pus of patients whose pneumonia had been previously treated with sulfadiazine were found to possess varying but definite degrees of sulfonamide-resistance.

notes

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Current Comment

PENICILLIN AS AN INHALANT

Under the auspices of the Long Island Biological Association Bryson, Lansome and Laskin [1] studied the behavior of penicillin as an inhalant. With a standard glass nebulizer a solution of the sodium salt of penicillin was readily nebulized for inhalation. Experiments on rabbits and on human beings demonstrated that in such form penicillin passed through the respiratory tract and appeared in the urine. In rabbits penicillin was recovered from the lung tissue after inhalation. As penicillin is bacteriostatic for pneumococci, streptococci and staphylococci in extremely high dilutions, its inhalation as an aerosol may be of advantage in the treatment of respiratory infections with these and perhaps also other bacteria. The results of further experiments will be of interest. The question also arises whether penicillin will be of value as an air disinfectant.

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PENICILLIN IN THE TREATMENT OF MENINGITIS

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Reports in the literature pertaining to the clinical effects of penicillin in the treatment of meningitis have in general been confined to observations on small groups of patients or on isolated cases.[1] No definite conclusions may be drawn from them concerning the efficacy of penicillin, the most satisfactory method of treatment or the minimum adequate dosage requirements. However, from in vitro studies demonstrating the pronounced sensitivity of the meningococcus, Streptococcus haemolyticus, pneumococcus and some strains of Streptococcus viridans to the action of penicillin, this agent should prove to be of considerable therapeutic value in the management of such infections, particularly in individuals who are sulfonamide resistant or sulfonamide reactors.

In a preliminary report [2] on 31 patients with cerebrospinal fever, we recorded 30 recoveries following the combined intrathecal and intravenous or intramuscular use of penicillin and concluded that penicillin is a safe, effective and highly potent agent in the treatment of this disease. Since then we have treated 40 additional patients with meningitis without a fatality. We are presenting at this time a report of our observations on this entire group of 71 patients.

MATERIAL

Cerebrospinal Fever.—Sixty-five patients in this series presented clinical evidence of cerebrospinal fever (table 1). In almost all patients the onset was sudden, with rapidly developing headache, nausea, vomiting and cervical rigidity of eight to forty-eight hours' duration. Twenty-four patients were semicomatose and 21 were comatose. The temperature on admission ranged between 99 (rectal) and 108 F. (rectal); the average for the group was 102.7 F. (rectal). Petechiae were found in 48 instances, and in 4 of these a purpuric rash was also noted. One patient with most extensive purpura presented the clinical picture of the so-called Waterhouse-Friderichsen syndrome. Two other patients who went into shock shortly after admission exhibited widespread petechial eruptions without purpura. Acute arthritis was observed in 15 of the patients on admission. The spinal fluid was turbid in all except 4 patients, and the initial spinal fluid cell count ranged from 21 to 50,100 leukocytes per cubic millimeter. The average cell count for the group was 11,700 per cubic millimeter, 88 per cent being polymorphonuclear leukocytes. In 49 patients meningococci were recovered from the spinal fluid, and in 10 of these the blood cultures were positive. In another patient with clinical evidence of fulminating meningococcemia the blood culture was positive although the spinal fluid was sterile and contained only 66 leukocytes per cubic millimeter. In the 3 other patients with clear spinal fluid on admission, meningococci were found in the spinal fluid on culture.

Owing to a lack of serums we were unable to determine the type of meningococci isolated from this group of patients. In 15 patients the clinical picture and spinal fluid findings were characteristic of meningococcic meningitis, but the stained smears and cultures of the spinal fluid revealed no organisms.

Meningitis Due to Other Bacteria.—In 3 patients hemolytic streptococci were recovered from the spinal fluid (table 2). In one of these a bacteremia was present, and in another bilateral acute otitis media was found. Two of these patients were semicomatose on admission. The spinal fluid cell counts ranged between 1,000 and 2,290 leukocytes per cubic millimeter.

There were 2 patients with Streptococcus viridans bacteremia and meningitis, both of whom were comatose on admission. Although the initial spinal fluid cell count was 450 leukocytes per cubic millimeter in each instance, in 1 it rose to 25,600 within ten hours.

In 1 patient with acute otitis media complicated by meningitis, pneumococci were cultivated from the spinal fluid. This patient was semicomatose on admission and

Read before the Section on Experimental Medicine and Therapeutics at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.
This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

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2. Rosenberg, D. H., and Arling, P. A.: The Treatment of Cerebrospinal Fever with Penicillin: A Preliminary Report, U. S. Nav. M. Bull., August 1944.

TABLE 1.—*Cerebrospinal Fever*

Patient	Age	Duration	Coma	Semi-coma	Petechiae	Temperature	Blood Culture	Spinal Fluid: Culture	Spinal Fluid: Cell Count	Spinal Fluid: Per Cent Polymorphonuclears	Penicillin (Units): Intrathecal	Penicillin (Units): Intravenous and/or Muscular	Complications
1	18	25 hr.	+	—	3+	104	0	+	50,100	98	125,000	860,000	
2	18	24 hr.	+	—	3+	104.8	0	+	15,000	92	100,000	900,000	Polyarthritis; thrombophlebitis
3	25	2 days	—	—	3+	101.6	0	+	8,000	98	45,000	340,000	
4	19	?	+	—	4+	108	+	+	7,200	90	55,000	380,000	Hydrocephalus; circulatory failure (autopsy)
5	23	26 hr.	+	—	3+	103.8	0	0	19,800	98	15,000	400,000	
6	20	1 day	—	—	1+	100.8	0	+	17,500	90	25,000	715,000	Fibrinous pericarditis; arthritis
7	69	2 days	—	+	0	104.2	0	0	8,600	89	25,000	280,000	
8	18	1½ days	—	+	3+	100.2	0	+	4,800*	75	15,000	260,000	
9	21	43 hr.	—	—	1+	102.4	0	+	11,100	100	10,000	235,000	
10	18	1½ days	—	—	0	101.4	0	0	12,800	92	10,000	180,000	
11	18	5 days	—	—	0	104	0	0	1,500	90	10,000	80,000	
12	20	48 hr.	—	+	2+	99.8	0	0	10,100	94	10,000	110,000	Transient diplopia, 4th day
13	18	29 hr.	+	—	1+	105	0	+	10,400	90	10,000	60,000	Acute otitis media, 3d day
14	18	17 hr.	+	—	0	102.4	+	+	21,000	94	10,000	40,000	Acute tonsillitis
15	20	2½ days	—	+	0	104.8	0	0	3,800	70	10,000	20,000	
16	18	3½ days	—	+	0	105	0	+	11,500	85	30,000	40,000	Sixth nerve palsy and paresis
17	19	1 day	+	—	3+	105.6	0	+	5,000	100	10,000	40,000	Epididymitis; arthritis
18	28	12 hr.	—	+	2+	103	0	0	6,600	89	10,000	20,000	
19	17	30 hr.	+	—	2+	102	0	+	17,300	99	50,000	290,000	Polyarthritis
20	18	21 hr.	—	—	0	99.8	+	+	14,100	96	30,000	40,000	
21	24	20 hr.	—	—	4+	103.8	+	0	66	94	None	250,000	Waterhouse-Friderichsen syndrome
22	29	40 hr.	—	+	1+	105.2	0	0	5,100	90	10,000	40,000	
23	27	34 hr.	—	+	2+	103.4	0	+	23,500	99	20,000	90,000	Epididymo-orchitis; diplopia
24	20	40 hr.	+	—	3+	105	+	+	13,100	93	10,000	90,000	Epididymo-orchitis; arthritis; diplopia
25	18	24 hr.	—	+	2+	103.2	0	+	14,800	92	20,000	90,000	
26	20	26 hr.	—	+	1+	101	0	+	11,400	95	30,000	115,000	
27	19	22 hr.	+	—	2+	105.2	0	+	18,700	100	20,000	155,000	
28	18	2 days	—	—	1+	104.2	0	0	6,000	92	10,000	100,000	Arthritis; acute tonsillitis
29	18	7½ hr.	+	—	0	104.8	0	+	18,700	93	10,000	100,000	
30	19	15 hr.	+	—	1+	102.4	0	0	8,100	94	10,000	90,000	Polyarthritis
31	18	1 day	+	—	3+	104.8	0	+	12,650	89	40,000	200,000	Epididymitis; polyarthritis
32	19	1 day	+	—	1+	103.8	0	0	12,100	100	10,000	70,000	
33	29	24 hr.	+	—	3+	103.6	+	+	22,500	96	30,000	70,000	Sixth nerve paresis
34	17	10 hr.	—	+	4+	102	+	+	2,000	100	50,000	250,000	Polyarthritis
35	18	15 hr.	—	+	2+	105.2	0	+	12,100	94	10,000	140,000	Polyarthritis
36	19	2 days	—	—	1+	102.6	0	0	6,200	68	10,000	40,000	
37	18	12 hr.	—	+	1+	104	0	+	2,500*	91	10,000	100,000	
38	22	2½ days	+	—	0	101.6	0	+	31,600	95	40,000	170,000	Thrombophlebitis
39	18	24 hr.	—	—	3+	101	0	+	4,260	90	20,000	100,000	Acute tonsillitis
40	20	16 hr.	—	+	3+	101	0	+	12,500	91	20,000	160,000	
41	17	7 hr.	+	—	0	103	0	+	10,800	99	20,000	140,000	
42	18	43 hr.	—	+	0	103.6	0	+	12,200	96	20,000	50,000	
43	18	46 hr.	—	—	1+	101.8	0	0	8,600	63	10,000	40,000	
44	18	4 days	—	+	4+	103.8	0	+	6,400	90	30,000	50,000	
45	32	1 day	+	—	2+	99.4	+	+	8,650	98	30,000	50,000	Epididymo-orchitis; arthritis
46	18	1 day	—	—	4+	102.2	0	+	7,900	94	20,000	100,000	Epididymitis, bilateral
47	35	17 hr.	—	+	4+	100.4	+	+	280	96	50,000	250,000	
48	26	2 days	—	+	4+	100.2	+	+	24,100	80	40,000	200,000	
49	18	1 day	—	—	3+	102	0	+	11,600	92	20,000	200,000	
50	21	1 day	+	—	0	102.6	0	+	21,600	96	20,000	200,000	Epididymitis
51	18	1 day	+	—	3+	100.6	0	+	12,700	97	20,000	200,000	
52	18	3 days	—	+	0	102	0	+	11,400	96	20,000	200,000	
53	18	1 day	—	+	1+	102.6	0	+	12,200	95	30,000	200,000	
54	18	4 days	—	—	0	100.8	0	+	9,300*	90	30,000	200,000	Acute tonsillitis
55	18	2 days	—	—	1+	101.8	0	0	9,200	95	10,000	200,000	
56	18	19 hr.	—	—	1+	102.6	0	+	3,200	98	30,000	335,000	Polyarthritis
57	18	15 hr.	—	+	1+	104	0	+	11,300	97	20,000	70,000	
58	18	8 hr.	—	—	0	103.6	0	+	255	88	10,000	None	
59	29	1 day	+	—	2+	99.8	0	+	20,400	100	50,000	50,000	Polyarthritis
60	18	2 days	—	—	0	102	+	+	2,000	96	20,000	50,000	
61	21	1 day	—	—	3+	100.2	0	+	21	0	20,000	230,000	Epididymo-orchitis; arthritis
62	25	1 day	—	+	3+	99	0	+	10,100	92	50,000	55,000	Arthritis; epididymitis
63	18	1 day	—	+	0	100.2	0	0	2,900	96	10,000	50,000	
64	27	12 hr.	—	+	2+	103.6	0	+	6,000	87	20,000	40,000	Epididymo-orchitis
65	23	2 days	—	—	1+	99	0	+	47,100	96	40,000	60,000	

* Cell count inaccurate owing to pellicle formation. In all cases the temperature was taken rectally. All patients were males.

the maximum temperature was 105.2 F. (rectal). The initial spinal fluid cell count was 1,100 leukocytes per cubic millimeter.

METHOD OF TREATMENT

Rammelkamp and Keefer [3] have demonstrated that penicillin administered intravenously does not appear in the spinal fluid. Injected intrathecally,[4] penicillin is slowly absorbed from the subarachnoid space and may be detected in the spinal fluid thirty-one hours later. It is more rapidly absorbed from the spinal fluid of patients with meningitis but may be found in significant amounts twenty-four hours after injection.

For purposes of investigation our plan of treatment varied somewhat in different patients, particularly from the standpoint of dosage. The most satisfactory method of treatment was found to be the following:

1. The initial diagnostic lumbar puncture was performed in the usual manner and the spinal canal was drained. Ten thousand Oxford units of sodium penicillin, dissolved in 10 cc. of isotonic solution of sodium chloride, was slowly introduced into the subarachnoid space. Penicillin (10,000 units) was administered intrathecally at twenty-four hour intervals until clinical improvement, sustained fall in temperature and/or a decrease in the meningeal signs were manifest and until the stained smears and cultures of the spinal fluid revealed no organisms. As penicillin was injected intrathecally with each lumbar puncture without awaiting the results of the bacteriologic studies, this plan in effect was tantamount to administering an additional dose of penicillin after the spinal fluid became sterile. We felt that in some instances it was unsafe to withhold treatment pending the results of the spinal fluid cultures. The persistence of coma was regarded as an indication for further intrathecal therapy. In the most severe infections and in those in which coma lasted forty-eight hours or longer, intrathecal penicillin was continued until the spinal fluid was bacteria free on three successive days. It is of paramount importance to drain the spinal canal as completely as is feasible before injecting penicillin. In several instances the spinal fluid was so viscous that aspiration was necessary.

2. Penicillin was also administered either by the continuous intravenous drip method at the rate of 5,000 units per hour or intramuscularly in doses of 15,000 units every three hours, the dose being reduced to 10,000 units every three hours if improvement was satisfactory. Generally, penicillin was given intravenously (40 units per cubic centimeter in a 5 per cent dextrose solution) for the first eight hours and continued intramuscularly thereafter. Patients with the fulminating type of cerebrospinal fever received penicillin intravenously at the rate of 10,000 units per hour for four hours initially. Owing to a lack of technical facilities the treatment could not be controlled by determinations of the amount of penicillin in the blood and spinal fluid. Instead, frequent clinical observations were made and the temperature, pulse and respirations were recorded every two hours.

In addition to specific therapy, 3,000 cc. of fluid was given daily. To combat shock in patients with fulminating meningococcemia, supportive therapy was given in the form of whole blood, plasma, epinephrine and desoxycorticosterone acetate. Oxygen therapy was employed when indicated.

RESULTS

Cerebrospinal Fever.—Sixty-four of the sixty-five patients in this group recovered. The one fatality occurred in a patient who was admitted in a moribund state with clinical and bacteriologic evidence of meningococcemia and with well advanced meningitis. His temperature was 108°F., pulse rate 140 and respiratory rate 66 per minute. He received 12 Gm. of sodium sulfadiazine parenterally in addition to 55,000 units of penicillin intrathecally and 380,000 units intravenously and intramuscularly but died thirty-eight hours after admission. Necropsy disclosed suppurative meningitis, secondary hydrocephalus and edema of the brain and lungs.

In the 64 patients who recovered, progressive improvement was noted soon after penicillin therapy was begun and was generally signalized by the disappearance of the restlessness, stupor and delirium, cessation of vomiting and an abrupt fall in the temperature and pulse rate. Those who were comatose usually regained consciousness within two to twenty-

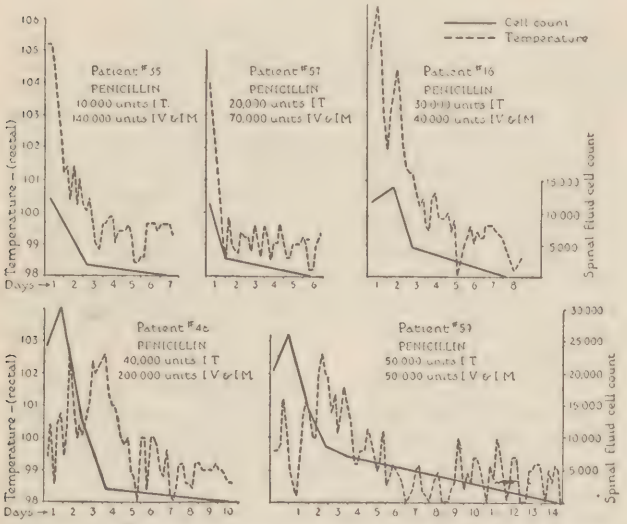
3. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.
4. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342 (March) 1943.

TABLE 2.—*Meningitis Due to Other Bacteria*

							Spinal Fluid			Penicillin (Units)	
Patient	Age	Duration	Coma	Semi-coma	Temperature	Blood Culture	Culture	Cell Count	Per Cent Polymorphonuclears	Intrathecal	Intravenous and/or Muscular	Complications
						A. Streptococcus Haemolyticus						
66	27	3 days	—	+	103.8	+	+	2,300	93	20,000	400,000	
67	27	22 hr.	—	—	104.4	0	+	1,700	79	20,000	170,000	
68	25	4 days	—	+	101.4	0	+	1,000	85	20,000	650,000	Bilateral acute otitis media
						B. Streptococcus Viridans						
69	18	3½ days	+	—	104.6	+	+	450	85	40,000	300,000	Acute pharyngitis
70	24	3 days	+	—	102	+	0	25,600 450	95 97	30,000	200,000	
						C. Pneumococcus						
71	35	4 days	—	+	102	0	+	1,100	84	30,000	800,000	Acute otitis media

In all cases the temperature was taken rectally. All patients were males.

four hours, but in 5 coma persisted for thirty to forty-eight hours and in 1 for four days. In 22 patients the temperature returned to normal within eight to seventy-two hours. In 16 a low grade intermittent fever (100 to 100.2 F. rectal) remained until the seventh day. In some of the latter patients as well as in those who exhibited a more prolonged febrile course the fever was found to be caused by one or more complications rather than by the meningitis, for the spinal fluid had become sterile and either gave a normal cell count or showed a residual lymphocytosis. Of the 4 patients whose temperature did not fall abruptly, 3 represented very severe infections and 1 showed signs of acute pericarditis and polyarthritis. Headache disappeared within two to four days and the signs of meningitis subsided completely in two to seven days (average, four days) except in our first 2 patients, who received 100,000 to 125,000 units intrathecally. In the latter the meningeal signs persisted for nine days. Generally there was a prompt reduction in the spinal fluid cell count, as shown in the accompanying chart, and the protein and sugar returned to normal rapidly. In all but the most severe infections this was accompanied by a disappearance of the polymorphonuclear leukocytes within four to seven days. In many a slight



Effect of penicillin on the temperature and spinal fluid cell counts of patients with cerebrospinal fever treated with 10,000, 20,000, 30,000, 40,000 and 50,000 units (total) intrathecally and various amounts intravenously and intramuscularly. Cases representing different grades of severity were selected. In patient 59, fever was prolonged by the presence of arthritis. The increase in the spinal fluid cell count in patients 16, 48 and 49 following the first injection of penicillin intrathecally was noted in 8 other patients. I. T., intrathecal; I. V., intravenous; I. M., intramuscular.

lymphocytosis remained until the tenth to the fourteenth day. In a few of our first patients a recurrence of fever was observed on the fourth to the sixth day if intrathecal penicillin was discontinued too soon. This was controlled by an additional dose of penicillin. As a rule the patients were able to be out of bed on the eighth day unless prevented by complications.

The amount of penicillin administered intrathecally to these patients varied with the severity of the meningeal infection. Thus, 42 patients recovered following only one or two injections of penicillin, 10 required three injections and 9 received four to five injections intrathecally. Through a lack of knowledge of the potency and effectiveness of penicillin, the first 2 patients whom we treated received nine and eleven injections respectively, totaling 100,000 to 125,000 units. Another patient with fulminating meningococcemia recovered with intravenous and intramuscular therapy alone, but in this instance the spinal fluid was sterile and showed only 66 leukocytes per cubic millimeter. The first 8 patients whom we treated received an intrathecal dose of 15,000 units dissolved in 15 cc. of isotonic solution of sodium chloride initially, but in view of the symptoms and signs of meningeal irritation resulting therefrom the 10,000 unit dose was employed thereafter. It is noteworthy that the amount of intrathecal penicillin necessary for recovery cannot be correlated with the initial spinal fluid cell count. Instead, it seems to depend on the number, type and virulence of the organisms as well as on the immunologic reaction of the host.

An analysis of the bacteriologic effects of penicillin on the spinal fluid obtained twenty-four hours after an intrathecal injection discloses that of 48 patients with positive cultures on admission in 29 the spinal fluid was sterile after one injection of penicillin, in 8 after two injections, in 3 after three injections and in 4 after four injections. However, in 2 others, both with very severe infections, the spinal fluid was sterile after one injection of penicillin but again showed meningococci twenty-four hours after the second injection. In 1 of these the spinal fluid remained sterile after the third injection and in the other after the fifth injection. Further, in 2 patients receiving penicillin every twelve hours the spinal fluid cultures were sterile after the first injection of penicillin, yet the direct smears showed organisms until two and five injections, respectively, were given. These findings suggest that sufficient penicillin is present in the spinal fluid after twelve hours, and occasionally after twenty-four hours, to inhibit the growth of bacteria on the culture medium. It is important, therefore, to correlate the bacteriologic findings with the clinical course and to observe the criteria set forth in our plan of treatment.

The total amount of penicillin administered intravenously and/or intramuscularly varied considerably (20,000 to 900,000 units), the first patients treated receiving the largest amounts. We soon observed that the total dosage could be reduced considerably without risk to the patient. Thus, 55 patients received between 20,000 and 250,000 units of penicillin intravenously and intramuscularly, and 35 of these received 100,000 units or less. One patient, seen several hours after the onset of his illness, recovered without any penicillin intravenously or intramuscularly. Among the patients without bacteremia, no appreciable difference in the outcome and course of the disease was perceptible in the group treated with 20,000 to 50,000 units when compared with those receiving as much as 900,000 units. Nor was there any correlation between the amount of penicillin given by these routes and the amount of intrathecal penicillin required for recovery. Of 10 patients in whom positive blood cultures were found, in 4 the blood was sterile after 40,000 to 50,000 units, in 5 after 70,000 to 125,000 units and in 1 after 250,000 units. In 2 of these the blood was sterile after 105,000 to 110,000 units, but in each penicillin was continued

until 200,000 units had been given. As 250,000 units was administered to the patient with the "Waterhouse-Friderichsen syndrome" this dose may represent the maximum amount required to combat the severe forms of meningococcemia unless circulatory failure is too far advanced when the patient is admitted to the hospital.

Acute monarthritis or polyarthritis was present in 15 patients on admission and was uninfluenced by the intravenous and intramuscular administration of as much as 900,000 units of penicillin. In 9 individuals aspiration of the affected knee joints revealed cloudy yellow fluid containing 20,000 to 100,000 polymorphonuclear leukocytes per cubic millimeter. In 8 the aspirated fluid was sterile, while, in the other, meningococci were found on direct smear and on culture. Intra-articular penicillin (10,000 units) was administered to 2 of the patients with sterile synovial fluid, but no beneficial effects were observed. In the patient from whose joint meningococci were recovered, the fluid became sterile after the intra-articular injection of 10,000 units of penicillin on two successive days.

Acute epididymitis, alone or with orchitis, developed in 10 patients. It usually appeared on the sixth to the seventh day of illness, although it was noted as early as the second day and as late as the tenth day. Its occurrence was unrelated to the amount of penicillin administered intravenously and intramuscularly. Three patients were treated with 150,000 to 160,000 units of penicillin over a period of forty-eight hours after the onset of acute epididymo-orchitis, but in none was the period of resolution shortened. In these as in the other 6 patients, spontaneous recovery ensued.

In 3 patients transient diplopia was observed without manifest cranial nerve involvement. Left sixth nerve palsy developed on the second day of admission in 3 of the most severe cases encountered in this series; in 1 of these it was followed twenty-four hours later by paresis of the right sixth nerve. In 2, restoration of function was ultimately complete; in the other, slight diplopia on extreme abduction remained. In 1 patient with fulminating meningococcemia slight transient third nerve paresis was noted. Acute fibrinous pericarditis was found on admission in 1 patient and was unaffected by 715,000 units of penicillin given intravenously and intramuscularly. In 4 patients acute tonsillitis and in another unilateral acute otitis media complicated the convalescence. In 2 instances acute thrombophlebitis of the saphenous vein developed on the fifth and sixteenth days, respectively, and was unrelated to the site of therapy.

Hemolytic Streptococcus Meningitis.—All 3 patients with meningitis due to hemolytic streptococci recovered completely following two intrathecal injections of penicillin. The spinal fluid was sterile twenty-four hours after the first injection, and the temperature returned to normal in four to six days. The patient with bacteremia was given 400,000 units intravenously and intramuscularly over a period of fifty-three hours. Blood drawn for culture on the fifth day was sterile. One of the patients without bacteremia received only 170,000 units of penicillin intravenously and intramuscularly over a period of thirty-nine hours. The temperature returned to normal within six days. The other patient with meningitis secondary to bilateral acute otitis media was given 650,000 units of penicillin intramuscularly over a period of eight and one-half days, although the temperature was normal in five days. No surgical intervention was necessary in this instance.

Streptococcus Viridans Meningitis.—Both patients recovered from meningitis, one following three and the other after four intrathecal injections of penicillin. The blood cultures were sterile in 1 patient after 40,000 units intravenously and in the other after 130,000 units intravenously and intramuscularly. However, penicillin was continued until 200,000 and 300,000 units, respectively, had been administered over periods of three to four days. The temperature returned to normal after three to five days. No sequelae were demonstrable, though both patients were comatose for twenty-four hours after therapy was begun.

Pneumococcic Meningitis Secondary to Acute Otitis Media.—Although there was only 1 patient with pneumococcic meningitis in our series, it is of interest that complete recovery followed three intrathecal injections of penicillin and 800,000 units given intravenously and intramuscularly over a period of ten and one-half days. The spinal fluid cultures remained positive until the third intraspinal injection of penicillin was administered. In view of the presence of acute otitis media and the possibility of bony suppuration in the areas adjacent to the middle ear, intramuscular penicillin was continued until the temperature remained normal for five days. Convalescence progressed uneventfully thereafter without surgical intervention.

UNTOWARD EFFECTS

In those patients who received penicillin intrathecally every twelve hours, as well as in some individuals who were given intrathecal doses of 15,000 units, more severe and more persistent headache was noted, fever was prolonged and signs of meningitis subsided more slowly. The irritating effect of penicillin on the meninges, when injected intrathecally, was previously demonstrated by Rammelkamp and Keefer [4] and by Pilcher and Meacham.[5] Further, we observed that penicillin produced by different manufacturers caused various degrees of meningeal irritation. Thus, the dark brown product was found to have the greatest irritant effect and caused febrile reactions, whereas the pale yellow product had the least demonstrable irritant effect. It is our belief, therefore, that the dark brown powder should not be used intrathecally. Localized thrombophlebitis developed in 4 patients at the site of the continuous intravenous injections but was of minor significance. In 3 patients with cerebrospinal fever mild transitory urticaria was noted within twenty-four hours after therapy was started. Whether this should be ascribed to the penicillin or to the disease per se cannot be stated. No other local or toxic effects were observed.

COMMENT

The effectiveness of penicillin in the treatment of meningococcic infections in man is clearly demonstrated by the recovery of 64 out of 65 patients with cerebrospinal fever. That penicillin is also a potent agent in the control of meningitis caused by Streptococcus haemolyticus, Streptococcus viridans and pneumococcus is indicated by the recoveries observed in our small

series of 6 patients. Contrary to the reported experiences with other infections, relatively small amounts of intravenous and/or intramuscular penicillin (40,000 to 250,000 units) were required to sterilize the blood stream in our cases of meningococcemia. Further, it was not necessary to continue penicillin for long periods of time, eight to forty-eight hours of therapy being adequate for these patients. It seems logical to assume that, when combined with intrathecal therapy, these data are equally applicable to the treatment of the nonbacteremic cases, the larger doses being employed in the more serious types of infection. On the other hand, in meningitis secondary to otitis media, intravenous or intramuscular penicillin must be continued until all other sources of infection have been adequately controlled. The majority of patients with cerebrospinal fever received only one or two injections of penicillin intrathecally, whereas in the most severe infections as much as five injections were necessary for recovery. It would appear safer, however, to administer a minimum of two intrathecal injections of 10,000 units each to all patients, even though many of the milder or earlier infections may be controlled by a single injection. As 2 patients without bacteremia recovered following only 20,000 units intravenously and 10,000 units intrathecally, and another recovered with intrathecal therapy alone, the question may be raised whether any intravenous or intramuscular penicillin is indicated in the nonbacteremic cases. Since the clinical picture presented by patients with bacteremia is often indistinguishable from that observed in individuals with negative blood cultures, it is our belief that penicillin should be administered intravenously or intramuscularly to all patients with meningitis. Moreover, it is of the utmost importance to continue penicillin intrathecally until recovery is assured, observing the criteria outlined in our plan of treatment. The findings of Pilcher and Meacham [5] in experimental meningitis support the latter contention.

The failure of penicillin to alter the course of arthritis or pericarditis was not unexpected. Similar failures have been observed with sulfonamide therapy.[6] It is probable that neither of these agents is excreted into these spaces in sufficient amounts, if any, to be effective. The occurrence of epididymitis, with or without orchitis, in 10 patients with cerebrospinal fever is of interest, as it is generally regarded as rare. However, it has been found quite frequently in some epidemics [7] and has also been observed following sulfonamide therapy.

We are fully cognizant of the shortcomings of any therapeutic agent requiring intrathecal administration to achieve its maximum effectiveness. Notwithstanding, it is evident from our experiences that for those patients who develop reactions to the sulfonamides, or in whom sulfonamide therapy is contraindicated for other reasons, for those who are sulfonamide resistant and for those with the fulminating bacteremias wherein a highly potent agent is indicated, penicillin alone may prove life saving. It is not unlikely that, when ultimately prepared in a more concentrated and more highly purified form, free from pyrogens, penicillin may be excreted into the subarachnoid spaces in sufficient amounts following intravenous or intramuscular administration to justify the abandonment of intrathecal therapy. Until then, penicillin should be administered intrathecally as well as intravenously or intramuscularly in the treatment of meningitis.

5. Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infections: III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin, J. A. M. A. **123**: 330 (Oct. 9) 1943.

6. Jaeger, H. W.: Meningococcic Infection of Joints, Rev. chilena de pediat. **14**: 414 (June) 1943. Rundlett, E.; Gnassi, A. M., and Price, P.: Meningococcic Meningitis: Prognostic Significance of the Spinal Fluid Sugar, J. A. M. A. **119**: 695 (June 27) 1942.

7. Brinton, D.: Cerebrospinal Fever, Baltimore, Williams & Wilkins Company, 1941, p. 51.

SUMMARY AND CONCLUSIONS

1. Penicillin was administered intrathecally and intravenously or intramuscularly to 65 patients with cerebrospinal fever (11 with bacteremia), 3 patients with hemolytic streptococcus meningitis (1 with bacteremia and 1 with acute otitis media), 2 patients with streptococcus viridans bacteremia and meningitis and 1 patient with pneumococcic meningitis secondary to acute otitis media. Seventy of the 71 patients recovered. Except for slight unilateral paresis of the sixth cranial nerve in 1 patient, no sequelae were observed.

2. Although one intrathecal injection of 10,000 units controlled some of the milder or earlier infections, a minimum of two injections is advocated as a precautionary measure. In the severe infections as much as five intrathecal injections (50,000 units) were required. Bacteremia was controlled by 40,000 to 130,000 units of penicillin intravenously and intramuscularly in the majority of instances. In a patient with fulminating meningococcemia and "Waterhouse-Friderichsen syndrome," 250,000 units over a period of forty-eight hours was followed by recovery. In meningitis secondary to otitis media more prolonged intravenous or intramuscular therapy is indicated.

3. Intravenous and intramuscular penicillin is ineffective in the treatment of such complications of meningococcemia as acute arthritis, epididymitis, orchitis or pericarditis.

4. Penicillin administered both intrathecally and intravenously or intramuscularly is an effective, highly potent agent in the treatment of meningitis. No significant untoward effects are demonstrable.

ADDENDUM.—Since the preparation of this paper penicillin was administered to 11 other patients with cerebrospinal fever. All of them recovered. For 2 patients who had manifested symptoms of meningitis for one week prior to hospitalization, six intrathecal injections of penicillin (60,000 units) were required.

ABSTRACT OF DISCUSSION

DR. WALLACE E. HERRELL, Rochester, Minn.: In view of the sensitivity of Neisseria intracellularis to penicillin, it is not surprising that such satisfactory results have been obtained. In 90 per cent of certain cases recovery will follow the use of sulfadiazine or one of the other sulfonamides. Penicillin, however, is an agent which appears relatively free of any serious toxic reactions. When greater supplies of penicillin are available it seems likely that it may be possible, as well as desirable, to treat all of these patients with penicillin without waiting for failures to occur with sulfonamides. This might well result in even greater success than has been attained in the past. It is my opinion that meningitis due to the several organisms isolated in 6 of the 71 cases reported by the authors will be found to respond in a less satisfactory manner to penicillin. It is the experience at the present time that probably no better recovery

rates than 60 per cent have been experienced with penicillin. The plan of treatment which has been outlined is an exceedingly satisfactory one. In addition to being administered by the intrathecal route, penicillin also should be given intramuscularly or intravenously in cases of meningitis. It is interesting that Rosenberg and Arling have found that relatively small amounts of penicillin (250,000 units) have been satisfactory. In meningitis due to pneumococci or streptococci I believe that larger amounts of penicillin will be required for the total dose and that the course of treatment will necessarily be somewhat longer. In connection with the arthritis complicating meningococcic meningitis, it is at times difficult to isolate the organism from the joint fluid. Nevertheless I am inclined to believe that there was definitely some beneficial effect. A positive culture was obtained in only 1 of 9 cases of septic arthritis in which cultures were made. Using Fleming's modification of the Wright slide cell technic, my associates and I have made determinations of the concentration of penicillin in the joint fluid of patients receiving this agent. In many instances we have found satisfactory antibacterial amounts of penicillin in the joints. The ratio of blood to joint fluid content is approximately 2 to 1. Urticaria or irritative dermatitis has been observed by us in 2 of 150 cases. I believe this skin reaction will be observed more frequently as more and more penicillin is used. Many people are sensitive to molds and to mold products. One must exercise caution in the presence of irritative dermatitis or severe urticaria. Continuing to force penicillin might result in the development of an exfoliative dermatitis, although at times one may administer penicillin without difficulty to patients who have previously exhibited this reaction.

Lieutenant Commander David H. Rosenberg (MC), U.S.N.R.: Dr. Herrell's comments regarding arthritis are of interest. Our observations were based on the duration of the symptoms and signs of arthritis. It is apparent that the effects of penicillin in these complications should also be studied by assays of the penicillin content of the affected joints.

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14 *Clinical Notes, Suggestions and New Instruments*

INTRAVENTRICULAR PENICILLIN IN THE TREATMENT OF STAPHYLOCOCCIC MENINGITIS

Captain William S. McCune and Captain Jack M. Evans
MEDICAL CORPS, ARMY OF THE UNITED STATES

Several reports have appeared in the literature of the use of penicillin intrathecally, with good results. Rammelkamp and Keefer [1] treated 6 patients with intrathecal penicillin, including 2 with brain abscess and meningitis and 2 with meningitis. In 2 of the patients who died, penicillin was demonstrated in the cerebrospinal fluid removed from the third ventricle and from the cisterna magna. They suggested an initial dose of not more than 10,000 Florey units, followed by subsequent doses of 5,000 units every twenty to twenty-four hours. Absorption and excretion were more rapid in patients with meningitis than in those without meningitis. There were no reactions to the intrathecal penicillin except as evidenced by an increase in the number of leukocytes in the spinal fluid and an occasional headache.

A discussion arising from the death of a patient with streptococcic meningitis who had been treated with penicillin intrathecally produced the suggestion by Lieut. Col. R. G. Spurling of the neurosurgical service that the drug might not be reaching the infection within the ventricles in sufficient concentration. In the case to be reported, after the clinical course had reached a standstill under intrathecal administration, it was decided to inject the chemotherapeutic agent directly into the ventricles to insure maximum levels within the brain.

Dosage and Cell Counts During Treatment

Date	Intrathecal Penicillin Units	Ventricular Penicillin Units	Spinal Fluid Cell Counts	Temperature, F.	White Count
6/26	.....	.....	23,750	105	9,200
6/28	17,500	.....	6,480	103.8	8,100
6/29	15,000	.....	4,400	104.8	7,600
6/30	10,000	.....	2,200	101.2	.....
7/ 1	10,000	.....	2,980	100.4	.....
7/ 2	10,000	.....	5,280	100.4	7,600
7/ 3	10,000	.....	2,475	101.4	7,600
7/ 4	10,000	.....	2,080	101	.....
7/ 5	7,500	7,500	.....	102	5,200
7/ 6	5,000	.....	.....	101	.....
7/ 7	5,000	6,000	675	103	7,300
7/ 8	.....	.....	170 (ventricular)	101	12,200
7/10	.....	.....	345	100.4	9,500

A brief survey of the literature reveals no reported cases of this method of penicillin administration. It is thought noteworthy that in this case the intraventricular injection of the drug was effective and produced no apparent harmful reaction. It should be emphasized that this method of treatment is recommended only for those patients who have failed to respond to intraspinal penicillin therapy.

REPORT OF CASE

A sergeant aged 25 had been well and free from symptoms until the evening of June 12, 1943. At that time, while riding a bicycle along a highway near Minersville, Pa., he was struck by an automobile and rendered unconscious.

He was taken to the Pottsville Hospital, where physical examination is said to have revealed an irregular swelling on the right forehead, pupils which were equal, dilated and reacted poorly to light, and an abrasion on the left shoulder. The temperature was 99.4 F. Physical and neurologic examination except for moderately deep unconsciousness were otherwise negative.

Blood studies were within normal limits. X-ray films of the skull showed a linear fracture in the right frontal bone starting 1 cm. from the midline and extending into the right frontal accessory nasal sinus.

Throughout the following two weeks the patient remained semiconscious, irrational, restless and incontinent of urine. He was said to have recognized his wife on one occasion. Temperatures varied from normal to 102.4°F. (axillary), pulse rates from 72 to 102. Lumbar puncture was said to have revealed blood tinged spinal fluid under a pressure of 330 cm. of water on June 23. The neurologic findings did not change materially from day to day. Treatment included only routine nursing care, 50 per cent dextrose twice daily and sulfathiazole 1 Gm. every four hours for two days. He was transferred to Walter Reed General Hospital on June 26.

On arrival at this hospital he was unconscious, restless and uncooperative, and remained so throughout the following six days. The temperature on arrival was 103 F. (rectal) and soon rose to 105, the pulse rate 128, respiratory rate 24. Neurologic examination was negative except for moderate rigidity of the neck, a positive Kernig sign, absent abdominal reflexes and positive Babinski and Gordon signs on the right.

A spinal puncture yielded cloudy fluid with an initial pressure of 180 cm. of water. Dynamics were normal. The fluid contained 23,750 leukocytes and 90 per cent polymorphonuclears. Cultures showed coagulase positive Staphylococcus aureus. The

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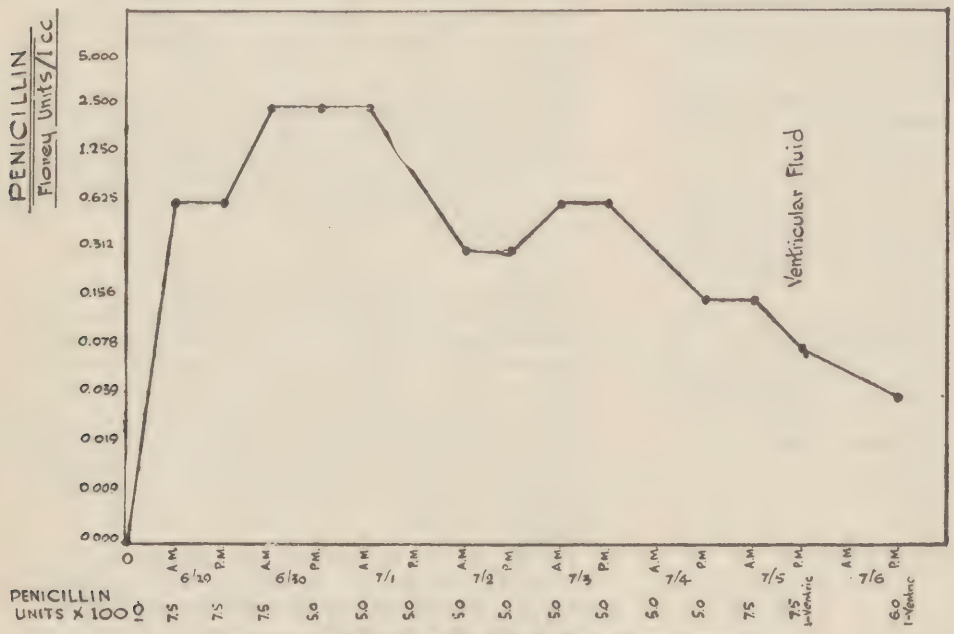
From the Neurosurgical Section and the Laboratory Section, Walter Reed General Hospital, Washington, D. C.

1. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342 (March) 1943.

white blood cell count was 9,200, red blood cell count 4,000,000, hemoglobin 94 per cent, and nonprotein nitrogen 25 mg., blood sugar 101 mg. and chlorides 495 mg. per hundred cubic centimeters. The urine had a specific gravity of 1.011, no albumin, no sugar and a normal sediment. An electroencephalogram showed the dominant rhythm to be slow, but there was no evidence of focalization.

Treatment and Course.—On admission sodium sulfadiazine 5 Gm. was administered intravenously, followed by 2.5 Gm. every twelve hours for two days. On June 28, however, the temperature was still 103.8 F. (rectal) and the pulse rate 118. Spinal tap showed an initial pressure of 210 cm. of water with cloudy fluid containing 6,480 leukocytes, 90 per cent polymorphonuclears and a positive culture for Staphylococcus aureus. Consequently, intrathecal penicillin was begun, with an initial dose of 10,000 Florey units. This was followed by subsequent doses of 7,500 units intrathecally twice daily for three doses, then 5,000 units twice daily for five days. No untoward reactions were noted. The state of unconsciousness remained unchanged, but the temperature dropped to 101.4 F. and the pulse rate to 92. The number of leukocytes in the spinal fluid dropped to 2,200 on June 30 and the culture became sterile. However, the spinal fluid cell count fell only slightly beyond that point, and on July 5, after seven days of intrathecal penicillin, the temperature rose to 102 F. In view of the possibility of an epidural abscess of the brain, bilateral burr holes in the posterior parietal area were made, but no collection of epidural fluid or pus was found. A needle was then passed into the right ventricle and 8 cc. of slightly turbid, colorless fluid withdrawn, which showed only minimal bacteriostatic activity in spite of the fact that 7,500 units of penicillin had been introduced by lumbar puncture two hours earlier. Seven thousand five hundred Florey units of penicillin was then dissolved in 5 cc. of saline solution and introduced into the ventricle. The galea and skin were closed. There was no immediate reaction to the procedure. On the following day, July 6, the temperature had fallen to 101 F. and the pulse rate to 80. On July 7 the temperature rose again to 103 F., the pulse rate to 104. Spinal tap resulted in fluid which was much clearer and contained only 675 leukocytes, with 65 per cent polymorphonuclears. The culture of this fluid was sterile. The right ventricular fluid removed contained only 170 leukocytes, with 59 per cent polymorphonuclears. The temperature on the following day was 101 F. but thereafter was never higher than 100.4 F.

Because of the shortage of the therapeutic agent, penicillin was stopped on July 7 and sodium sulfadiazine begun with an initial intravenous dose of 5 Gm., followed by 2.5 Gm. every twelve hours until July 11. From July 11 to July 18, 4 Gm. of sulfadiazine was given daily by mouth, and on July 18 all medication was stopped. After the withdrawal of penicillin and the change to sulfadiazine the spinal fluid cell count rose to 345 cells on July 10 and 665 cells on July 12 but then gradually fell to a count of 17 cells with 4 per cent polymorphonuclears on July 26. On that day, through a right frontal burr hole exploration, a small, old, subdural hygroma containing about 14 cc. of clear, yellow, sterile fluid was evacuated.



Penicillin levels in the spinal fluid by Rammelkamp's method.

During this course of treatment the patient's mental state gradually improved to a level at which he was able to recognize friends, eat with help, read large type and carry on a very simple conversation. At last report he was able to play rummy, read the comic strips and go to the bathroom with help. The meningitis has been cured. After July 14 his temperature remained normal and neurologic examination showed no abnormal findings. There were no pronounced changes in the urine or blood counts during treatment.

SUMMARY AND CONCLUSIONS

This case of staphylococcic meningitis treated with intrathecal and intraventricular penicillin is presented chiefly to show that intraventricular use of penicillin as an adjunct to the intrathecal route of administration is possible without untoward reactions and with good effect. The fact that there was evidence of only minimal passage of penicillin from the spinal canal into the ventricles in two hours reemphasizes the fact that the normal flow of cerebrospinal fluid may hinder the free passage of therapeutic agents from the spinal canal into the ventricular system. This is especially true in meningitis when arachnoid adhesions and exudate may partially obstruct the normal spinal fluid pathways. The introduction of penicillin directly into the ventricles overcomes this handicap and insures a more uniform distribution of the therapeutic agent throughout the cerebrospinal fluid system. The dosage used in this case was not large and in the light of future knowledge may prove to have been too small. The levels of penicillin in the spinal fluid during treatment are shown on the graphic chart. The introduction of a needle into the ventricle in the acute stage of meningitis should be performed with caution, and not until penicillin has been given intraspinally for several days.

15 TREATMENT OF OSTEOMYELITIS OF THE FACIAL BONES WITH PENICILLIN

WILLIAM M. M. KIRBY, M.D.
AND
VIRGIL E. HEPP, M.D.
SAN FRANCISCO

One of the most serious complications of sinusitis is osteomyelitis of the facial bones. This may occur either following surgical operation or by direct extension from the diseased sinuses. In either instance the outlook has always been very poor, for, in spite of sulfonamides and operative intervention, the infection tends to extend throughout the bone and to spread to the brain and meninges, with a mortality in severe cases of as high as 80 per cent. With penicillin, however, there was every reason to think that the prognosis might be greatly altered, for this powerful bacteriostatic agent might hold the infection in check until adequate surgery could be performed. The cases reported here, in which brilliant results were obtained, showed that such was the fact and are reported because they illustrate the technical problems both of penicillin administration and of surgical treatment.

CASE 1.—*Development of cellulitis and osteomyelitis following intranasal maxillary antrotomy; no response to sulfonamides; prompt response to penicillin, with three relapses; complete cure after removal of all necrotic bone.*

Mrs. M. W., a woman aged 32, housewife, who entered Stanford Hospital on Sept. 24, 1943, had had chronic sinusitis for four years, and four weeks before entry a right intranasal maxillary antrotomy was performed. A week later pain and swelling developed in the soft tissues overlying the antrum. A wisdom tooth was removed, allowing pus to drain into the mouth through the empty socket, but the pain and swelling of the face did not subside. Sulfathiazole 6 Gm. a day for two weeks was administered in another hospital with no improvement. On entry the temperature was 38.5 C. (101.3 F.), pulse rate 86, respiratory rate 16 and blood pressure 115/70. The patient, a slender woman in good general physical condition, was very uncomfortable because of the pain and swelling of the face. The right eye was nearly shut, and the swelling extended down to the mouth, obliterating the nasolabial fold. The overlying skin was red and glistening, and there was definite fluctuation just below the eye. In the mouth, thick yellow pus was draining from the empty tooth socket and from a small fistula in the center of the hard palate. The right nostril was filled with thick yellow purulent exudate. Apart from these local findings, physical examination revealed no abnormalities.

The red blood cell count was 4,100,000; hemoglobin, 70 per cent; white blood cell count; 12,200, with a normal differential count; the erythrocyte sedimentation rate (Wintrobe) was 44 mm. per hour; packed cell volume was 38, and the urine was normal.

Details of the course in the hospital are shown graphically in the accompanying chart. The day following entry a continuous intravenous infusion of penicillin was begun, and two hours later an operation was performed. Widespread destruction of the right maxilla required extensive removal of the lateral and inferior aspects of the maxilla, including the hard palate nearly to the midline. The antrum was filled with pus, and the pterygoid plate, roof and posterior wall of the antrum were removed. The soft tissue abscess of the face was found to drain freely into the space left by removal of bone, and for this reason no external incision was made. Devitalized bone was removed as completely as possible, the sharp edges were smoothed, and the entire cavity was packed with iodoform gauze.

Cultures of bone removed at operation revealed a heavy growth of anaerobic nonhemolytic streptococci. Sections of the bone showed areas of necrosis and inflammation indicative of subacute osteomyelitis.

Administration of penicillin 200,000 units a day by continuous intravenous infusion in 1 liter of isotonic solution of sodium chloride was continued during operation and afterward for five days, a total of 1 million units. Two transfusions and fairly heavy sedation were the only other therapeutic measures. There was, during this five day period, a dramatic diminution of the swelling and tenderness of the face, but a recurrence was predicted because denuded, apparently necrotic, maxillary bone could be palpated with forceps along the infraorbital ridge, high in the cavity left by the operation.

Three days after the penicillin was stopped there was a sudden reappearance of pain and swelling below the right orbit, and an external incision 4 cm. in length was made parallel to, and 0.5 cm. beneath, the lower margin of the orbit. The soft tissues were edematous, but little frank pus was encountered. Cultures revealed large numbers of both anaerobic nonhemolytic streptococci and Staphylococcus aureus (coagulase positive). The underlying maxillary bone was denuded of periosteum, but no bone was removed because definite sequestration had not yet occurred. The wound was packed open with iodoform gauze and pencillin therapy was begun by the continuous intravenous route, 50,000 units a day. A severe febrile reaction, probably caused by pyrogenic saline solution in which the penicillin was mixed, necessitated a change to the continuous subcutaneous route after 175,000 units had been administered. A total of 810,000 units was given intravenously and subcutaneously during this course of eleven days. Again the swelling and tenderness disappeared completely, and very little pus was present in the wound. Cultures were repeatedly positive for S. aureus (coagulase positive) and anaerobic nonhemolytic streptococci.

After five days penicillin therapy was instituted for the third time because of a recurrence of swelling, tenderness and pus at the local site. A pure culture of anaerobic nonhemolytic streptococci was obtained from the pus. After seven days' treatment by the subcutaneous route approximately 100,000 units daily, the patient was again operated on. In addition to extraction of all remaining portions of apparently devitalized maxillary bone along the infraorbital ridge, the right upper central incisor and the remainder of the right side of the hard palate were removed. There was again a severe postoperative febrile reaction, probably due to impurities in the penicillin solutions. The penicillin was discontinued two days after the operation, a total of 900,000 units during this ten day course, and a final total of 2,690,000 units since entry. The temperature quickly returned to normal, and this time the swelling and tenderness did not recur. The facial incision healed rapidly, and the patient left the hospital ten days after the last operation. Cultures of the cavity in the mouth still revealed a heavy growth of anaerobic nonhemolytic streptococci and S. aureus (coagulase positive).

During a six months follow-up period the patient has remained entirely well and is now having a prosthesis made to replace the bony structures which were removed surgically.

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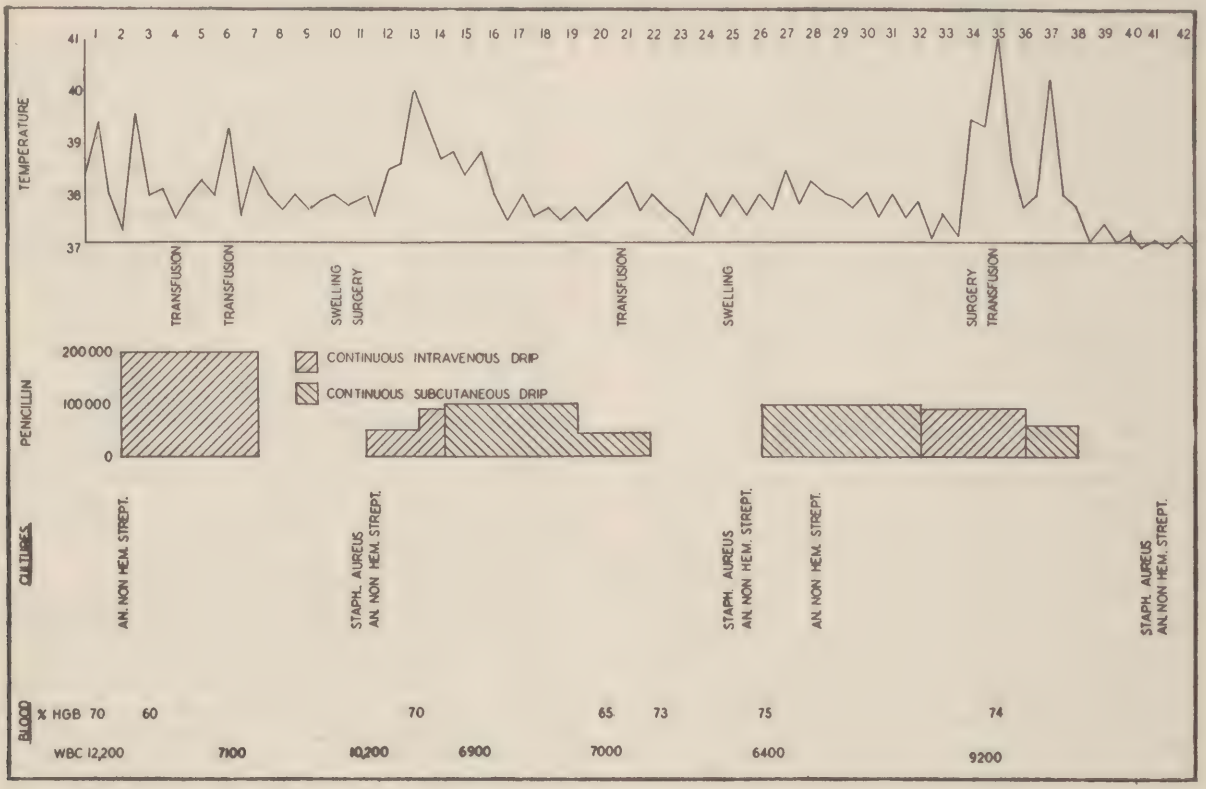
The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigation recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

CASE 2.—*Failure of sulfonamides and extensive surgical procedures to cure osteomyelitis of maxillary bone following sinusitis; prompt response to penicillin, with several relapses; complete cure with penicillin plus removal of all foci of dead bone.*

B. P., a man aged 23, a dyecaster, who entered the San Francisco City and County Hospital in December 1942, suffered from acute right frontal sinusitis and osteomyelitis of the frontal bone. Surgical exploration revealed a widespread purulent destruction of the frontal bone and a large extradural abscess. Approximately one-half the frontal bone was removed to well beyond the limits of infected bone, and both frontal sinuses were obliterated. The T shaped incision was packed open for the following two months, during which time convalescence was uneventful. A secondary closure of the wound was then accomplished with excellent healing except for a small persistent fistula in the midline at the juncture of the flaps. Three months after entry the patient was discharged and thereafter followed regularly in the Stanford University outpatient clinic. All attempts to close this fistula met with failure. Repeated x-ray studies revealed a persistent left anterior ethmoiditis and after much investigation it was felt that the fistula was being fed by this ethmoid infection. In July 1943 the patient entered Stanford Hospital, where external ethmoidectomy and excision of the fistulous tract was performed. S. aureus was cultured from the operative area. Convalescence was uneventful, and the patient was discharged on the sixth postoperative day. Twelve days after the operation he complained of frontal headache and pain in the left malar region. Examination revealed tender swelling along the left infraorbital ridge and swelling of the operative wound with slight fluctuation. The patient reentered the hospital, where the wound was opened widely, releasing a small amount of purulent discharge. Palpation of the depths of the wound with forceps revealed the frontal process of the left maxilla to be denuded of periosteum, and S. aureus was again isolated from the pus. These findings seemed to indicate an osteomyelitic process proceeding along the superior ramification of the left maxilla. Full doses of sulfadiazine (6 Gm. a day) were given over the following eighteen days, and supportive treatment consisted of blood transfusions, vitamin therapy and a high calory diet. Excellent drainage was secured from the infected area. In spite of this treatment the patient's temperature was septic; he appeared very toxic and continued a steady downhill course. The left intraorbital swelling progressed slowly until the left eye was entirely closed and the malar swelling extended into the left temporal region. X-ray examination revealed an early destructive process extending along the left infraorbital ridge laterally to the infraorbital foramen.

S. aureus and anaerobic nonhemolytic streptococci were cultured on two occasions from pus expressed from beneath the swollen area through a small opening just below the medial side of the left orbit. Since sulfonamide therapy seemed inef-



Course in case 1.

fectual in controlling the spread of the disease, penicillin was begun on August 30 by continuous intravenous drip, 60 units per cubic centimeter, a total of 50,000 units in seventeen hours. Because of venous thrombosis, a change was then made to the continuous subcutaneous route, 100,000 or 200,000 units daily, a total of 1,385,000 units in twelve days. There was decided subjective improvement within twelve hours after the penicillin was started, and during the next ten days the pain and swelling disappeared completely. Daily cultures revealed S. aureus and anaerobic nonhemolytic streptococci for five days, S. aureus alone for the next three, and thereafter the drainage ceased altogether.

Five days after penicillin was stopped the pain and swelling recurred, accompanied by a temperature rise to 38.2 C. (100.7 F.) and white blood cell count of 9,600. Penicillin was started intravenously 200,000 units daily for five days, and the incision below the medial side of the left eye was extended laterally 1 centimeter beyond the infraorbital foramen. Pus obtained at the operation contained only anaerobic nonhemolytic streptococci. Again the swelling and pain promptly sub-

sided, but penicillin therapy was reinstituted after a four day interval, 100,000 units daily for three days, in conjunction with the surgical removal of a sequestrum through the facial incision. The patient then went home but returned again ten days later with swelling and inflammation below the left eye. After five days of continuous penicillin therapy, partly intravenous and partly subcutaneous (total, 320,000 units) he was clinically well and left the hospital because of the death of his mother. Two small sequestrums were removed from the outer edge of the wound during this hospitalization. Ten days later there was another typical recurrence, and this time packs soaked with penicillin 100 units per cubic centimeter were placed in the wound every three hours for four days. Surgical exploration revealed two more small sequestrums in the outer edge of the wound, but the underlying exposed bone appeared healthy when they were removed. The wound closed quickly when the packs were discontinued, and the patient went home on October 27, having received a total of 3,010,000 units of penicillin. He has been entirely well during a follow-up period of over five months.

CASE 3.—*Cellulitis of jaw following tooth extraction; involvement of orbit with protrusion and blindness, and osteomyelitis of frontal bone; cure with penicillin after failure with surgical procedures and sulfonamides.*

G. S., a white man aged 38, a farmer, developed a painful swollen right jaw in September 1943 three days after the extraction of two upper molar teeth. The cellulitis spread rapidly, causing protrusion and complete blindness of the right eye. On September 30 he was admitted to another hospital, where his temperature was 106 F., and x-ray examination showed clouding of the right antrum but no signs of osteomyelitis. After two weeks of therapy with full doses of sulfadiazine he went home much improved but returned four days later with a recurrence of fever, headache and periorbital swelling. X-ray examinations now showed involvement of the right sphenoid and ethmoid cells as well as of the right antrum. During the next two months he was given repeated courses of sulfonamides, and several subcutaneous abscesses below the right eye were drained surgically. On December 5 an incision was made through the right brow, releasing 5 cc. of creamy pus, and the underlying bone was covered with granulation tissue. It was felt that the infection had spread from the lateral wall of the right antrum up along the anterior portion of the lateral wall of the orbit. Staphylococcus albus (coagulase positive) was cultured from the pus. Following this operation there was again improvement, but he was transferred to Stanford Hospital when the pain and swelling recurred on December 20. The temperature was normal, but there was a definite protrusion of the right eye with eversion of the lower lid and conjunctivitis. A small abscess below the eye was drained and S. albus (coagulase positive) was again cultured. X-ray examination revealed cloudiness of the right antrum and ethmoids and both frontal sinuses. There were slight but definite osteomyelitic changes of the frontal bone in the region of the right temporal fossa, and pitting edema was noted over this area. A right intranasal antrotomy was performed, and penicillin was administered by the continuous intravenous route 200,000 units daily for eight days. Intramuscular injections of 15,000 units every three hours were then given for nineteen days, a total of 3,650,000 units by both routes. During this time the redness, pain and swelling disappeared altogether, although the proptosis remained and the x-ray changes persisted. After three weeks at home he returned on Feb. 15, 1944 with a corneal ulcer and diffuse conjunctivitis of the right eye, resulting from insufficient protection afforded by the everted lower lid. In addition to local treatment he received 840,000 units of pencillin intramuscularly over a period of a week. During a follow-up period of two months there has been no evidence of recurrence of infection, and the cornea has been protected by dark glasses and merthiolate ointment. A plastic repair of the lid will be performed at a later date.

CASE 4.—*Osteomyelitis of frontal bone and brain abscess following sinusitis; stormy course with convulsions and paralysis of the left arm and leg following surgical operation; cure with prolonged penicillin therapy and aspiration of a second brain abscess.*

During the second week of December 1943 J. C., a white man aged 51, developed acute frontal sinusitis with severe headache and photophobia. The pain became progressively worse in spite of chiropractic treatment, and a swelling of the soft tissues appeared above the right eye. A typical grand mal seizure on Jan. 12, 1944 prompted transfer to Stanford Hospital, where the patient was found to be semistuporous and had a temperature of 40.5 C. (104.9 F.). There was stiffness of the neck, but no abnormal reflexes were elicited. Pitting edema was noted over both eyebrows, especially on the right. The white blood cell count was 22,400 and the spinal fluid contained 1,000 cells per cubic millimeter, all polymorphonuclears. Both the blood and the spinal fluid were sterile at this time. A continuous intravenous infusion of penicillin was begun, 100 units per cubic centimeter, and at operation he was found to have right frontal sinusitis with osteomyelitis, extradural and subdural pus, and an abscess of the right frontal lobe. The affected bone was removed as completely as possible, and drains were placed in the abscess cavity. The whole area was irrigated with penicillin solution, and the wound was covered with penicillin saturated gauze. Anaerobic nonhemolytic streptococci were cultured from the right frontal sinus and brain abscess. Postoperatively penicillin was administered by the continuous intravenous route 300,000 units daily for eight days, and the head wound was irrigated two or three times daily with penicillin 100 units per cubic centimeter. During this time the course was stormy, with continued high fever, clonic convulsions at frequent intervals, periods of Cheyne-Stokes respiration and a flaccid paralysis of the left arm and leg. On January 18 a few nonhemolytic streptococci were cultured from the spinal fluid, and the next day 10,000 units (1,000 units per cubic centimeter) of penicillin was instilled intraspinally. All other cultures of the spinal fluid were sterile. Penicillin was discontinued because of a generalized maculopapular erythematous rash, which appeared six days after therapy was instituted and became progressively worse. After fading promptly, the rash reappeared six days later, when 180,000 units of penicillin from the same manufacturer was administered intramuscularly in thirty-six hours. It again faded promptly and was apparently a dermatitis medicamentosa caused by a certain lot of penicillin. The patient remained disoriented and semicomatose and on February 2 passed into a deep coma, with irregular heart beat and respirations. Pus (8 cc.) was aspirated from a second brain abscess located posterior to the first in the prerolandic area; cultures again revealed anaerobic nonhemolytic streptococci. Penicillin 100 units per cubic centimeter was instilled into the cavity, and no pus was obtained when a second aspiration was attempted three days later. Since it seemed imperative, penicillin therapy was again started, preparations other than the preparation which had previously caused the rash being used, and this time there was no recurrence of dermatitis. The wound was irrigated three times a day with 5 and 10 cc. (100 units per cubic centimeter) and 15,000 units was injected intramuscularly every three hours. Beginning with the aspiration of the second brain abscess and the reinstitution of penicillin therapy there was slow but steady improvement. The spinal fluid, at first cloudy and under increased pressure, gradually cleared so that daily taps were no longer necessary. Convulsions ceased, the patient regained his mental faculties and the paralysis of the left arm and leg gradually disappeared. The exposed anterior pole of the right frontal lobe of the brain prolapsed through the wound at first and became covered with purulent granulations. As this tissue became necrotic it was gently wiped away with sterile gauze. The brain then gradually receded and for two weeks, from February 24 until March 9, a profuse leakage of cerebrospinal fluid occurred from the wound; this gradually decreased

and ceased spontaneously. Penicillin was finally discontinued on March 16, two months after the patient was admitted to the hospital. At this time the wound was clean and epithelium was beginning to cover the healthy granulation tissue. Mentally there was complete recovery, and the left arm and leg had regained much of their original strength. The total amount of penicillin administered locally and parenterally was 7,540,000 units.

CASE 5.—*Osteomyelitis of frontal bone following surgical operation for frontal sinusitis; failure to respond to sulfonamides, with fever and bacteremia; prompt response to penicillin; sequestrectomy later with a second course of penicillin.*

E. A., a man aged 53, developed a swelling over the right eye in March 1943, which subsided in four days. In September the pain and swelling recurred and this time did not respond to conservative therapy. On October 21 in another hospital both frontal sinuses were opened widely and the anterior ethmoid cells removed. Two weeks later the patient developed a low grade fever, headaches and edema over the frontal bones. Subacute osteomyelitis was diagnosed, and the process continued to spread in spite of intensive therapy with sulfonamides. He entered Stanford Hospital Jan. 21, 1944 with a temperature of 38.5 C. (101.3 F.), pitting edema over the forehead and a draining sinus above the medial side of the right eye. Anaerobic nonhemolytic streptococci were cultured from the blood and from the draining sinus; S. aureus (coagulase positive) was also isolated from the latter site. The blood count was normal, but both the blood and the spinal fluid Wassermann reactions were positive. X-ray examination showed an extensive widespread, moth-eaten destruction of the frontal bone, most pronounced on the right. A continuous intravenous infusion of penicillin was started January 22, 200,000 units daily for twelve days, a total of 2,400,000 units. Intramuscular injections were then given, 15,000 units every three hours for a week, a total of 760,000 units. For the first eight days, penicillin (100 units per cubic centimeter) was also injected into the draining sinus, 4 to 10 cc. twice a day. During this time his temperature subsided to normal, headache disappeared and drainage ceased. He left the hospital but returned on February 29 for the removal of several large sequestrums of the frontal bone through an incision just above the right eyebrow. In conjunction with surgical operation intramuscular penicillin was again given, 120,000 units daily for fourteen days, a final total of 4,847,000 units for both entries. S. aureus (coagulase positive) was cultured from the sequestrums, and sections showed changes characteristic of chronic osteomyelitis with sequestration. The postoperative course was uneventful, but x-ray examination revealed that not all of the sequestrums had been removed. The wound is now healed and the patient is entirely well, but the follow-up period of six weeks is too short to be sure that there will be no further recurrences. The course of the asymptomatic neurosyphilis will also be followed with great interest.

COMMENT

The fundamental principles underlying the treatment of osteomyelitis of the facial bones are well illustrated by these 5 cases. In contrast to the sulfonamides, penicillin prevents further spread of the infection, so that either before or after sequestration has occurred devitalized bone can be removed surgically. Relapses are likely to occur until all the necrotic bone is gone. Surgical procedures are probably best postponed until the patient has had three or four weeks of penicillin therapy and sequestration has occurred, since there is then a better possibility of removing all the devitalized bone at one time.

Penicillin dosage is still controversial. The first 2 patients were given small amounts for only a few days, as a result of which there were frequent relapses. Prolonged treatment with larger doses prevented relapses in the other 3 cases and possibly shortened the course of the disease. The present policy in this clinic is to administer 200,000 units daily by continuous intravenous drip for ten days to two weeks, followed by 15,000 units intramuscularly every three hours (120,000 units daily) for another two or three weeks. If surgical treatment is delayed until sequestration has occurred, penicillin should be continued for at least a week postoperatively.

The only toxic reaction observed was a generalized maculopapular rash (case 4), which appeared six days after treatment was begun and faded promptly when penicillin was discontinued. The rash did not recur when the patient was given penicillin prepared by a different manufacturer.

In cases 1, 2, 4 and 5 anaerobic nonhemolytic streptococci were probably primarily responsible for the osteomyelitis, with S. aureus (coagulase positive) also present in cultures from sinuses communicating with the skin. These same organisms were isolated by Williams and Nichols,[1] who also report excellent results with penicillin. S. albus (coagulase positive) was the only organism recovered in case 3.

The results in these 5 cases would seem to justify the hope that the present high mortality rate in cases of acute, subacute and chronic osteomyelitis of the facial bones will be drastically reduced when supplies of penicillin become generally available.

1. Williams, H. L., and Nichols, D. R.: Spreading Osteomyelitis of the Frontal Bone Treated with Penicillin, Proc. Staff Meet., Mayo Clin. **18**: 467 (Dec. 1) 1943.

STUDIES ON THE DISTRIBUTION OF PENICILLIN IN THE EYE 16

AND ITS CLINICAL APPLICATION

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The remarkable success obtained in the treatment of severe infections with penicillin has naturally called attention to possible applications in ophthalmology. In general, the drug has proved to be very effective in the treatment of infections produced by Staphylococcus aureus, the pneumococcus, the hemolytic streptococcus, the gonococcus and the meningococcus. With the exception of the last two mentioned organisms, penicillin is relatively ineffective against gram negative bacteria. Encouraging results already have been reported following its employment in cavernous sinus thrombosis, corneal ulceration, conjunctivitis,[1] orbital and facial cellulitis [2] and acute gonorrheal ophthalmia.[3]

In corneal infections experimentally produced with Staphylococcus aureus, Robson and Scott [4] found this drug to be very effective if applied within a reasonably short time. From these data they recommend that the local use of penicillin be given a clinical trial. Another investigator, von Sallmann,[5] produced intraocular infections in rabbits by introducing pneumococci and Staphylococcus aureus into the anterior chamber. It was very effective against the pneumococcus and Staphylococcus aureus but ineffective in combating the ensuing endophthalmitis after intralenticular injections of Clostridium welchi.

The only work that has been done on the penetration and distribution of penicillin has been its determination in a few of the body fluids. Florey and his co-workers have demonstrated its absorption and excretion in blood and urine. They found penicillin in the whole blood, bile and saliva but none in the pancreatic juice or tears of cats given the substance intravenously. They have shown that penicillin does not become inactivated when incubated for three hours with slices of kidney, spleen, brain, muscle, lymph gland, lung and intestine of rabbits. Rammelkamp and Keefer [6] have investigated the absorption and excretion of penicillin after intravenous, intramuscular and subcutaneous injections. They found that penicillin failed to penetrate red blood cells in significant amounts (less than 10 per cent of the plasma concentration) and that it failed to enter the spinal fluid, tears or saliva Von Sallmann and Meyer,[7] studying the penetration of the drug after local and systemic application, demonstrated penicillin in the aqueous humor; it was particularly high after iontophoresis. In two tests the vitreous humor was negative. When the administration was systemic, paracentesis led to a manifold increase in the secondary aqueous.

Since the efficiency of a chemotherapeutic agent depends not only on its potency but also on its diffusibility and concentration in the infected part, it was considered desirable that investigation be undertaken to secure information on the distribution of penicillin in the eye and other organs and body fluids.

EXPERIMENTAL STUDIES

A. *Distribution After a Single Massive Dose.*—General anesthesia was induced in dogs by the intravenous injection of sodium amytal (0.045 Gm. per kilogram of body weight). Then 12,800 units of penicillin per kilogram of body weight in a highly concentrated form (20,000 units per cubic centimeter solution) was injected intravenously. At specified time intervals blood samples were withdrawn, eyeballs enucleated and body tissues removed for analyses. Caution must be exercised in interpreting results, since the number of experiments performed was small. After removal of the eyeball the aqueous humor was aspirated and the globe dissected into the following components: lens, vitreous humor, cornea, sclera and chorioretinal layer. All tissues but the vitreous humor were immediately weighed and transferred to mortars, where they were thoroughly ground with sand mixed with a minimum volume of saline solution. It was found that no appreciable differences were obtained if the tissues were ground after rapid freezing or prepared in the usual manner. Each mixture was transferred quantitatively to a 15 cc. tube and centrifuged from five to ten minutes. The supernatant liquid and washings were combined and brought up to a specified volume. Aliquot portions were removed and assayed by the method developed by Florey and his associates. The Oxford writers admit that this test has a ± 25 per cent error, but they doubt if other methods are more accurate. They claim that their method has the advantage of being many times more rapid and can be carried out with small amounts of fluid. The vitreous humor (stirred vigorously until it became fluid), aqueous humor, blood and bile were tested without dilution.

Penicillin was found to penetrate into the eyeball with great rapidity. After fifteen minutes the penicillin content was found to be at its highest peak of concentration in the chorioretinal tissues and extraocular muscles. After the initial sharp rise, the aqueous humor and the relatively poorly vascularized conjunctiva and sclera showed a slow continuous increase until the end of the first hour. The blood penicillin was at its highest level directly after the injection and fell immediately. The concentration of penicillin was found to be in the following order: extraocular muscles, sclera, conjunctiva, blood, chorioretinal layer and the aqueous humor. The penicillin content of the vitreous humor and cornea was always less than 0.2 Oxford unit per gram of tissue, while the lens was consistently negative. The tears of dogs, contrary to the negative findings of Florey and his associates on the cat and of Rammelkamp and Keefer on man, showed a moderate concentration of penicillin (3.19 at fifteen minutes). The drug concentration in those tissues and fluids attaining the highest peak fell the most precipitously. Thus, in the first fifteen minutes the penicillin content of the extraocular muscle reached a concentration of almost 15 units per gram of wet weight, while at the end of sixty minutes it fell to about 6 units. On the other hand the penicillin content per gram of wet weight of the chorioretinal layer was 2.05 units in fifteen minutes and 1.39 units at the end of sixty minutes. At the end of three hours penicillin was completely absent from the blood, but the ocular fluids and media with the exception of the crystalline lens still showed a trace of this substance.

B. *Penetration into the Eye After the Parenteral Administration of Penicillin in Approximate Clinical Doses.*—Instead of employing a dosage far exceeding that employed clinically, dogs were given 1,500 units of penicillin per kilogram of body weight either by a slow intravenous drip over a period of five or six hours or divided into three intramuscular injections at two hour intervals. The blood tested at hourly intervals throughout the experiment was always negative. Likewise, the ocular fluids and tissues tested at the end of three, four, five and six hours were entirely negative with two exceptions, in which a trace was found: one was a sample of conjunctiva examined at the end of six hours of a continuous intravenous administration, and the other exception was a specimen of aqueous humor aspirated immediately after the third intramus-

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The laboratory investigation was carried out with the aid of Dr. K. K. Chen and his associates at the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis.

1. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**: 177, 1941.
2. Herrell, W. E.: Gramicidin and Penicillin, Surg. Clin. North America **23**: 1163, 1943.
3. Griffey, W. P.: Penicillin in Treatment of Gonorrheal Conjunctivitis, Arch. Ophth. **31**: 162 (Feb.) 1944.
4. Robson, J. M., and Scott, G. I.: Local Chemotherapy in Experimental Lesions of the Eye, Lancet **1**: 100, 1943.
5. von Sallmann, L.: Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infection with Pneumococcus, Arch. Ophth. **30**: 426 (Oct.) 1943; Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infections with Staphylococcus Aureus and Clostridium Welchi, ibid. **31**: 54 (Jan.) 1944.
6. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425, 1943
7. von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, Arch. Ophth. **31**: 1 (Jan.) 1944.

cular injection.

C. *Distribution of Penicillin in Eye After Subconjunctival and Topical Administration.*—If penicillin can readily reach the ocular media and tissues following its subconjunctival and topical application, a more effective and economical method of therapy might be achieved by local application rather than by intravenous administration. Since the effective dose for various infections is yet unsettled and the dosage of penicillin largely arbitrary, it was advisable to determine the tolerance of the ocular tissues to the subconjunctival and topical administration of penicillin.

The application of a 5 per cent solution of metycaine as a surface anesthesia preceded the subconjunctival injection of penicillin in rabbits. Penicillin in 500, 1,000, 2,500 and 5,000 units dissolved in 0.25 cc. of isotonic solution of sodium chloride was injected. With the exception of the eyeball receiving the 5,000 unit injection all globes showed a decreased amount of swelling in one hour, and the eyes were normal at the end of twenty-four hours except for the hyperemia at the point of injection. With the injection of 5,000 units, chemosis was pronounced at the end of one hour but at the end of twenty-four hours was greatly reduced. Since 2,500 units of penicillin was the highest concentration tested that was well tolerated, this quantity was used for the study of penicillin distribution following subconjunctival injection.

The reaction of the eyeball to topical applications of penicillin was tested on the corneas of rabbit and man. In the rabbit a constant contact of the cornea with a saline solution of penicillin containing as much as 20,000 units per cubic centimeter produced no staining with fluorescein or any other change visible to the naked eye. In man, solutions containing 10,000 units per cubic centimeter, dropped into the conjunctival sac produced only a slight smarting. Examination of the eyeball with the slit lamp and fluorescein staining revealed no alteration in the corneal epithelium.

(*a*) Subconjunctival Injection: After subconjunctival injections, eyeballs were removed at one-half and three hour intervals and the ocular tissues and fluids tested for the penicillin concentration. The penicillin content in the aqueous found with 2,500 units in this manner approximated that obtained by using forty times as much intravenously. The concentration reached in the cornea, vitreous humor, conjunctiva, sclera and iris with ciliary body exceeded many times that obtained by the intravenous route. Thus the cornea and vitreous humor, which barely showed a trace of penicillin when it was given intravenously by the subconjunctival route, reached the high value of 28 units in the cornea and 1.95 units in the vitreous humor (chart 3). One cannot rule out completely that leakage from the subconjunctival injection may lead to direct contact of the penicillin with the cornea. Unfortunately, after the intravenous injection the uveal and retinal tissues were not tested separately nor were they separated in anterior and posterior portions, so the value 2.03 units represents a mean of the entire retina and uvea. This value is in sharp contrast to the high values of 10.8 to 26.32 units per gram of iris and ciliary body obtained after the subconjunctival injection of much smaller amounts of penicillin. One disadvantage of the latter method is that the posterior uveal and retinal tissues showed little or no penicillin. Analyses of scleral tissue taken from the anterior portion of the globe gave values ranging from 163.23 to 194.40 units per gram, while those taken from the posterior portion of the globe showed a range from 92.54 to 93.31 units per gram. The conjunctival concentrations were extremely high, ranging from about 106 to 449 units per gram of tissue. In three hours most of the ocular tissues tested were essentially negative except for slight amounts in the aqueous and vitreous humors.

(*b*) Topical Application: Rabbits were anesthetized by intravenous injections of sodium amytal. An excess of solution containing 20,000 units of penicillin per cubic centimeter of isotonic solution of sodium chloride was placed in the conjunctival sac of the rabbit, and the lids were clamped sufficiently tight to prevent an escape of the fluid. At one-half, one and three hour intervals the eyes were irrigated with saline solution to remove any remaining penicillin. After enucleation of the eyeball, tests were made for the penicillin content in the manner already described. Chart 2 shows the rise in concentration of penicillin in the aqueous humor. It reaches a value of 3.32 units per cubic centimeter in thirty minutes, a level maintained with little change for one and one-half hours; but at the end of the third hour an increase in the concentration was noted (14.2 units per cubic centimeter). The aqueous humor at this time was of amber color, resembling a dilute solution of the type of penicillin used in the experiment, showing that penicillin penetrates not only the cornea but also the chromatic material that is combined with it. The concentrations of the drug in the cornea and iris with ciliary body are very high. Although the penicillin content of the sclera following topical application was less than that obtained by subconjunctival injection, it was very much greater than that found after the intravenous injection (chart 3). Of all three routes employed, the topical application in the form of a prolonged corneal bath gives the highest value in the vitreous humor. The crystalline lens was always negative by any method of administration.

It was reasonable to expect that wetting agents having a definite influence in increasing the penetrability of sulfonamides might have a similar effect in increasing the penetration of penicillin.[8] However, the results were negative with an aerosol. In fact, there was a moderate decrease when penicillin was used with this wetting agent. Whether this resulted from a destruction of penicillin by the aerosol due to p_H changes or from other factors was not determined. Other wetting agents should be investigated.

D. *The Effect of Paracentesis on the Penicillin Content of the Aqueous Humor.*—The effect of paracentesis on the amount of penicillin in the second aqueous was undertaken. Rabbits were anesthetized by intravenous injection of sodium amytal, and penicillin was injected intravenously. A moderate increase in the second aqueous was noted, confirming the observation made by von Sallmann and Meyer. In view of the fact that the aqueous was removed at fifteen and forty-five minute intervals, a period of time for the penicillin concentration to increase normally (chart 1), it is quite possible that this noted increase might have been independent of the paracentesis. The experiment should be

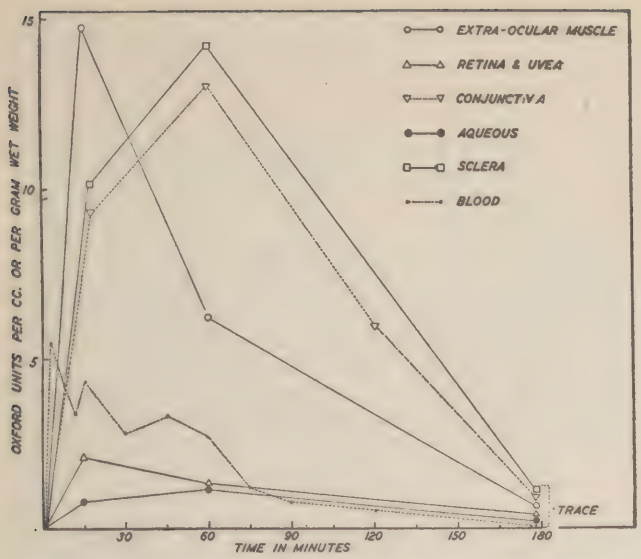

Chart 1.—Concentration of penicillin in the blood, ocular tissues and fluids following a single large intravenous injection (12,800 units per kilogram).

repeated with suitable controls.

E. *Penicillin in the Tears.*—Florey and his co-workers in England and Rammelkamp and Keefer in this

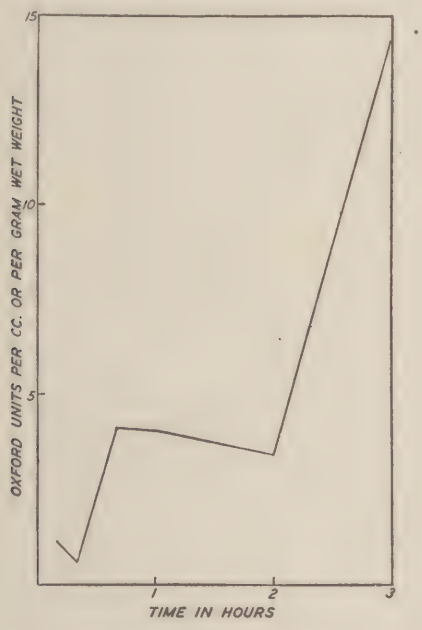

Chart 2.—Penetration of penicillin through the cornea.

country have reported the absence of penicillin in tears. After intravenous injection of 12,800 units of penicillin per kilogram of body weight the tears of dogs contained 3.15 units per cubic centimeter within fifteen minutes and 1.66 units per cubic centimeter within the secnnd fifteen minute period. The effect of lysozyme in tears was ruled out by testing tears

8. Bellows, J. G.: Chemotherapy in Ophthalmology, Arch. Ophth. **29:** 888 (June) 1943. Bellows, J. G., and Gutmann, M.: Application of Wetting Agents in Ophthalmology with Reference to Sulfonamide Compounds, ibid. **30:** 352 (Sept.) 1943. Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, ibid. **27:** 34 (July) 1942.

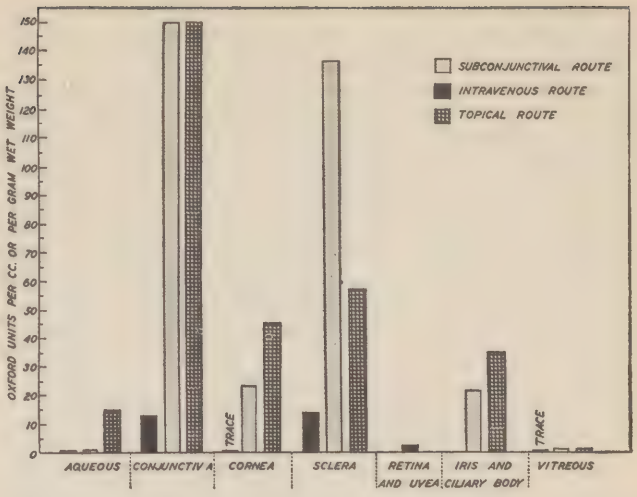

Chart 3.—A comparison of the maximal concentrations of penicillin in eyeball following intravenous, subconjunctival and topical administration.

before administering penicillin. However, the possibility of increased diffusion of serum and penicillin from the underlying capillaries due to conjunctival irritation must be considered.

F. *The Concentration of Penicillin in Other Body Tissues and Fluids.*—In dogs, after the intravenous injection of 12,800 units of penicillin per kilogram of body weight, various tissues and fluids were collected at the end of one, two and three hour intervals. Table 1 shows that the concentration in the tissue is greatest at the end of the first hour and falls to a trace or becomes entirely negative within two or three hours. This gives substantial support for the clinical recommendation that penicillin be administered either by intravenous drip over a long period of time or by frequent intramuscular injections.

G. *Clinical Trial of Penicillin in Ocular Infections.*—The foregoing data make it apparent that topical applications of penicillin are the most suitable form of administration for external infections of the eyeball and its adnexa and that parenteral injections, although leaving much to be desired, are best suited for infections of the uveal and retinal layers particularly in the posterior segment. Table 2 summarizes the results of the topical application of penicillin for external ocular infections. In a total of 13 cases, gratifying results were obtained by penicillin drops. The concentration of the drug varied from 200 to 2,500 units per cubic centimeter.

A less satisfactory response was observed in deep seated lesions even though penicillin was administered by intravenous or intramuscular injection. A total of 3 cases was studied. Two patients had chronic exudative choroiditis: one with a solitary lesion near the superior temporal periphery adjacent to an area of old healed chorioretinitis, and the other with a large confluent area of deep choroiditis in the inferior mid aspect of the fundus. Tuberculin tests in both cases were negative through the 1 to 10 dilutions. Syphilis and all possible foci of infection had been eradicated. The vitreous in both instances contained many opacities but not to such an extent as to prevent a view of the fundus lesions. Both patients were given a continuous

intravenous drip of 100,000 units of penicillin for seventeen hours (in 1,000 cc. of isotonic solution of sodium chloride). This was followed by 100,000 units of the drug daily by intramuscular injection for the next two days. The 100,000 units was dissolved in 20 cc. of isotonic solution of sodium chloride so that each cubic centimeter contained 5,000 units. This was administered every three hours day and night. At the end of the seventy-two hours treatment neither case showed evidence of clinical improvement. Penicillin in the strength of 500 units per cubic centimeter was instilled every three hours day and night for ten days. At the end of that time both patients were again examined.

TABLE 1.—*Concentration of Penicillin in Body Tissues and Fluids After a Single Massive Intravenous Injection*

Tissue	Time in Hours: 1 Hour — Units per Gm. or Cc.	2 Hours — Units per Gm. or Cc.	3 Hours — Units per Gm. or Cc.
Liver	4.77	*	*
Bile	6.65	..	4.99
Heart	2.41	..	*
Kidney	17.38	*	*
Lung	8.91	*	*
Voluntary muscle	1.90	*	*
Skin	6.06	*	*
Nerve	0	0	0
Brain	0 to *	0	0
Dura	0 to *	..	..
Bone marrow	0	0	0
Pancreas	2.69	..	*
Adrenal	2.72	0	0
Spleen	1.89	..	*
Buccal mucosa	8.39	*	0
Small intestine	9.68	..	0

Each figure represents two or more determinations.
* Equals trace of penicillin.

There was no appreciable change in the appearance of the fundus picture, vitreous opacities or visual acuity.

The third case was one of subacute bilateral iridocyclitis with a unilateral macular edema of the left eye. This patient's eye condition was believed to be due to a recent neisserian infection which had recurred on two occasions—once following a third course of sulfathiazole and once following an inadequate dose of penicillin. At this time the urethral discharge had entirely subsided and prostatic findings were negative. All foci of infection had been eliminated. The condition had progressed in spite of atropine and hot compresses locally and repeated intravenous injections of typhoid vaccine with a poor febrile response.

Prior to the intravenous and intramuscular administration of penicillin for three days as outlined, the visual acuity of the right eye was 20/20 and of the left eye 20/70. There were many cells in the aqueous of both eyes. At the completion of the therapy described the vision of the left eye had improved to 20/30. At that examination it was noted also that practically all the cells had disappeared from the aqueous of both eyes. One week later the vision had slipped in the left eye to 20/50 — 1 and a moderate number of cells were again present in the aqueous of both eyes. Pupillary dilatation had been maintained during this period.

This patient subsequently showed much improvement following two treatments in the fever cabinet, running the temperature up to 106 F. for five hours. One hundred thousand units of penicillin was administered intravenously over a period of a few hours during the fever therapy. The day following this first treatment the visual acuity of the left eye had improved to 20/20 — 2 Jaeger 1 and thereafter was staying at 20/15. All macular edema had subsided.

There was considerable clearing of the cells in the anterior chambers of both eyes following this regimen but there had been some slight recurrence of cells in the anterior chamber of the right eye during the past forty-eight hours.

Although the clinical data presented in this report are small, they bear out the conclusions reached theoretically that, in external disease in which local application of penicillin could be brought in high concentration on the infection, the infection cleared rapidly. Infections of the chorioretinal layers in which the penicillin concentration was slight even after massive intravenous dosage showed little response.

COMMENT

The ready permeability of most of the tissues after the intravenous injection of penicillin is undoubtedly an important factor in its therapeutic efficacy. However, some very important exceptions exist: the cornea, lens, vitreous humor, cerebrospinal fluid, nerve, brain, dura and bone marrow show little or no penicillin after such injections. In one experiment erratic results were obtained with bone marrow. It must be emphasized that some preparations of penicillin have enormous potency and are effective in dilutions of over 1 to 100 million. Since amounts less than 0.1 to 0.2 unit are not measurable by Florey's method, it is still possible that bacteriostatically effective concentrations may be present in some of these tissues and organs.

Certain organs and tissues apparently extract large amounts of this substance from the blood stream and eventually may contain a concentration greater than that of the blood. For example, the extraocular muscles contain almost 15 units per gram of wet weight within fifteen minutes, and the less vascularized tissues, such as the conjunctiva and sclera, obtain their maximum concentrations of 13 and 14 units per gram of wet weight at the end of sixty minutes. These values are about three times as high as that found in the blood at its peak, which is immediately after the injection. The data here presented suggest the possibility that some tissues may have a selective absorption for penicillin. The highest peak reached in the aqueous humor is at the end of one hour, resembling in this respect the conjunctiva and sclera. Both the aqueous humor and uveal and retinal tissues show but small amounts of penicillin, and therefore the decline is not as precipitous as in the case of those tissues which contain large amounts of penicillin (chart 1). The avascular cornea and vitreous humor either contained no penicillin or at the most showed a quantity less than 0.2 unit per gram of tissue. The factors that the lens is avascular and is surrounded by a capsule which may serve as a barrier are probably important in explaining its constant negative test.

The very high penicillin content in the kidney (17.38 units per gram) is not surprising in view of the fact that this organ is active in the excretion of the drug. Of possible clinical importance are the surprisingly high amounts found in the lungs (8.91 units per gram), skin (6.06 units per gram), buccal mucosa (8.36 units

per gram), small intestines (9.68 units per gram), bile (6.65 units per cubic centimeter) and liver (4.77 units per gram). The saliva, contrary to the negative report of Rammelkamp and Keefer, showed a slight amount of penicillin.

It is interesting to speculate where the penicillin is "lost." Florey and his associates have demonstrated that the entire loss cannot be accounted for by the amount appearing in the urine. It is noteworthy that the bile contains a very high concentration of penicillin. Even at the end of three hours, when all other tissues and fluids are either negative or show only a trace of the drug, the bile contained about 5 units of penicillin per cubic centimeter (table 1). The Oxford investigators incubating penicillin with blood and various tissues at 37 C. for three hours observed no decrease in the potency of the drug. The intravenous or intramuscular injection of penicillin in dogs in therapeutic dosage gives a concentration of penicillin in the blood and most tissues too small to be detected by the usual methods of assay. Since it is advisable to give penicillin in large doses so as to prevent organisms (particularly the staphylococci) from becoming penicillin fast, it seems from the data reported here that the dosage which is considered by some clinicians to be sufficient, that is, 100,000 units daily for a 70 Kg. person, is really inadequate.

When penicillin can be applied topically, an enormous concentration can be achieved locally, which surpasses by far any value which can be secured even by the most massive intravenous doses. This procedure has the further advantage of saving a considerable amount of the drug. Subconjunctival injection up to 2,500 units and topical administration of a concentration up to 20,000 units of penicillin are well tolerated by the rabbit. By these means extremely high concentrations can be obtained in the tissues of the anterior segment of the eyeball. It must be pointed out that the rabbit's cornea has been shown to be more permeable to sulfonamides than those of the dog and man. A similar difference may exist with penicillin. Whether this variation in permeability is due to the reported differences in the thickness of the cornea is unknown. Friede [9] states that the thicknesses of the central portions of the corneas of rabbit, dog and man are 0.8, 0.9 and 0.9 mm. respectively. At the periphery the thickness is even greater in man. However, the concentration reached in the anterior segment of the eyeball is so great that, even if the penetration in man should be only a small fraction of that found in the rabbit, the amount reaching the cornea, conjunctiva, sclera, aqueous and the anterior uvea will still be adequate for therapeutic effectiveness.

The amount of penicillin reaching the vitreous chamber, although slight, is much more than what can be obtained even after very massive intravenous doses. The extremely high corneal penetration reached after three hours of constant corneal bath with penicillin is surprising (chart 2). The constant moderate value for two hours followed by the rapid rise after that time suggests a change in corneal permeability permitting an increased penetration.

9. Friede, R.: Vergleichende Studien zur Grösse der tierischen und menschlichen Hornhaut mit besonderer Berücksichtigung der menschlichen Megalcornea, Arch. f. Ophth. **131**: 1, 1934.

TABLE 2.—*Results of Topical Application of Penicillin for External Ocular Infections*

Patient	Diagnosis	Cultures	Medication	Results
N. L. W.	Chronic catarrhal conjunctivitis O. U.; granular blepharitis	.....	Penicillin drops, 200 units per cc.	Conjunctivitis cured in 24 hours; blepharitis unimproved
W. W. W.	Acute catarrhal conjunctivitis	Gram negative diplobacilli and hemolytic Staph. albus	Penicillin drops, 500 units per cc.	Control eye treated with 0.25% zinc sulfate; penicillin treated eye cured in 48 hours; control eye cured in 72 hours
M. H.	Acute hypertrophic catarrhal conjunctivitis with follicles O. D.; no preauricular glands; 10 days later similar onset in O. S.	Two cultures negative; third culture showed 1 colony of nonhemolytic Staph. albus	Penicillin drops, 200 units per cc.: later 500 units per cc.	Right eye (first involved) required 10 days for clinical cure; left eye cured in 3 days on 500 units per cc. solution
H. C. B.	Acute catarrhal conjunctivitis O. S.	Few bacteria only, not identified	Penicillin drops, 200 units per cc.	Cured in 24 hours
J. B. C.	Acute catarrhal conjunctivitis O. S.; 2 days later similar condition O. D.	Pure culture; Strep. viridans	Penicillin drops, 500 units per cc.	O. S. very much improved in 24 hours; cured in 48 hours; O. D. cured in 36 hours
H. C. H.	Acute catarrhal conjunctivitis O. U.	No growth	Penicillin drops, 500 units per cc.	Both eyes cured in 48 hours
R. S. S.	Acute catarrhal marginal ulcer O. S.	Nonhemolytic Staph. albus	Penicillin drops, 200 units per cc.	Cured in 12 hours; patient had had similar episodes previously, not treated with anything, which resolved in 12-24 hours
D. B.	Acute catarrhal conjunctivitis O. D.	No growth	Penicillin drops, 500 units per cc.	Cured in 24 hours
H. B. G.	Chronic catarrhal conjunctivitis O. U.; 15 years' duration with recurrent bouts of pain, redness and tearing; allergic studies negative; somewhat improved O. U.; autogenous vaccine over 3 months' time	Staph. albus and diphtheroids	Penicillin drops, 500 units per cc.	Lids much improved in 72 hours; penicillin continued for 3 weeks; objectively and subjectively there was great improvement
C. F. H.	Right acute episcleritis 1 day's duration	.....	Penicillin drops, 2,500 units per cc.	Eye white in 24 hours
R. S.	Acute conjunctivitis O. D.; first noticed on awakening	.....	Penicillin drops, 2,500 units per cc.	Much improved in 24 hours; normal in 48 hours
C. M.	Acute catarrhal conjunctivitis O. U.	Hemolytic Staph. albus	Penicillin drops, 500 units per cc.	Much improved in 24 hours; normal in 48 hours
A. F. B.	Acute conjunctivitis	Culture and smears negative	Penicillin drops, 2,500 units per cc.	Objectively and subjectively normal

It would seem from the results of our investigation that, if the efficacy of the drug is dependent only on its concentration (an assumption for which there is no proof), the local application of penicillin to the eyeball should be effective in those infections with organisms susceptible to the action of penicillin, involving conjunctiva, cornea, sclera, anterior chamber, iris with ciliary body, and vitreous. Similar infections involving the posterior uvea and retinal layers will require the parenteral administration of large amounts of penicillin. But even after huge amounts the penicillin content in these tissues is low.

Bearing out these laboratory findings are the clinical results. Infections involving conjunctiva and cornea respond rapidly to penicillin locally. Infections involving the posterior uveal tissues seem uninfluenced even after massive intravenous doses.

SUMMARY

1. Penicillin can be detected in the eyeball within fifteen minutes after a large intravenous injection. The concentrations of the tissues and fluids examined, listed in decreasing order, are as follows: extraocular muscles, sclera, conjunctiva, tears, chorioretinal layer, aqueous humor, vitreous and cornea. The crystalline lens is negative. The value in the blood is highest immediately after the injection, drops to about half of the original level in one hour and is down to zero at the end of three hours. The extraocular muscle has its greatest concentration in fifteen minutes and drops precipitously from then on. The aqueous humor and the less vascularized tissues such as the conjunctiva and sclera after their initial sharp rise within the first fifteen minutes continue to increase slowly until the end of the first hour. Barely a trace of penicillin remains in the eyeball after three hours.

2. Penicillin administered intravenously and intramuscularly in amounts comparable to therapeutic doses ordinarily reaches such a slight concentration in the fluids and tissues that it is not measurable by the usual methods.

3. After subconjunctival injection, high and even enormous concentrations are reached in the cornea, iris with ciliary body, conjunctiva and sclera. There is a moderate amount in aqueous and vitreous humors. The posterior half of the chorioretinal layer and the lens show negative results. After a constant corneal bath of penicillin the results are similar, except that the concentrations in the aqueous, cornea, vitreous and iris with the ciliary body are higher and those in the conjunctiva and sclera are lower.

4. One hour after a huge intravenous injection of penicillin the body tissues and fluids examined, listed in decreasing order, are as follows: kidney, small intestine, lung, buccal mucosa, bile, skin, liver, adrenal, pancreas, heart, voluntary muscle and spleen. At the end of three hours all the tissues and fluids examined, except bile, show little or no penicillin. Bile at that time still retains 5 units of penicillin per cubic centimeter.

5. The clinical results of local application of penicillin in external ocular disease are encouraging. In a few deeply situated inflammatory lesions of the eye, little or no improvement is noted in spite of huge doses of penicillin given intravenously.

PENICILLIN TREATMENT OF CAVERNOUS SINUS THROMBOSIS

VICTOR GOODHILL, M.D., LOS ANGELES

A 5 year old boy with acute fulminating bilateral cavernous sinus thrombophlebitis made a complete recovery when treated with penicillin,[1] after showing no response to sulfonamide-heparin therapy.

Thrombophlebitis of the cavernous sinus is one of those diseases the mortal aspect of which has cast an ominous shadow over infections of the face and head. Prior to the advent of sulfonamide therapy, reports of recovery and "cure" of this disease were rare.

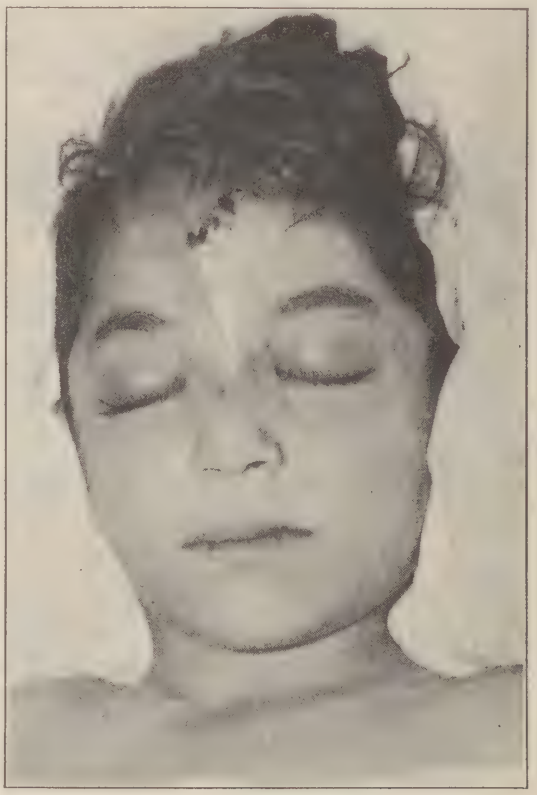

Fig. 1.—Appearance before administration of penicillin.

When sulfonamides were first introduced, isolated cases of recovery began to appear. The addition of heparin to sulfonamide therapy further improved the statistics for survival in this previously highly fatal disease.

The present case is interesting in that (1) no response was noted following therapy with heparin and sulfathiazole and (2) prompt clinical response followed therapy with penicillin.

REPORT OF CASE

History.—E. A., a 5½ year old Mexican boy, had a "pimple" on his forehead on Sept. 29, 1943. On October 1 he fell and struck his head in some sand. The "pimple" began to swell and became painful, and there was accompanying fever. On the following day his face and eyes became swollen. He was admitted to the Childrens Hospital on October 3.

From the Departments of Otolaryngology, University of Southern California School of Medicine, and Childrens Hospital.

1. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

Physical Examination.—On the day of admission, October 3, the child was acutely ill, in moderate distress and with a temperature of 104.6 F.

There was an open draining furuncle in the midfrontal region between the supraorbital region and the hair line. Both eyes were completely swollen shut by edema of the upper lids. There was slightly less edema of the lower lids. There was slight conjunctivitis but no chemosis; extraocular muscular function was perfect. The pupils were equal and regular and reacted to light and in accommodation. There was no proptosis. Fundus examination showed slight venous congestion. The frontal edema extended upward from the furuncle to about 2 cm. above the hair line.

There was no nuchal rigidity, and the reflexes were normal. There were no other significant conditions observed on physical examination.

Laboratory Observations.—X-ray study of the frontal sinuses and frontal bone showed no pathologic changes.

A blood count on October 4 revealed 31,500 leukocytes with 80 per cent neutrophils. The hemoglobin content was 82 per cent. The urine gave a 1 plus reaction for albumin.

Pus from the furuncle on culture yielded a coagulase positive nonhemolytic Staphylococcus aureus. Culture of blood taken on October 6 produced a growth of coagulase positive hemolytic Staph. aureus.

Diagnosis on Admission.—The diagnosis was furunculosis of the frontal region with probable thrombophlebitis of the frontal veins and superior branches of the facial veins.

Frank involvement of the cavernous sinus was not present on admission.

Course.—Immediately after the boy's admission oral administration of sulfathiazole in a dosage of 3 grains (0.2 Gm.) per pound (0.5 Kg.) in twenty-four hours was started. Hot compresses of a 1 per cent solution of sulfanilamide were applied continuously to the furuncle. On the second day, October 4, the frontal edema increased and began to involve the lower lids. The temperature curve was septic in character, reaching 106 F. The child became somewhat stuporous. On October 5 edema of the right lower lid became pronounced, and chemosis was noted in both eyes. Beginning engorgement of the retinal veins was apparent at the same time. Accordingly, it became obvious that the thrombophlebitic process was extending to the right and probably to the left cavernous sinus. In view of the lack of response to chemotherapy alone, a continuous drip of heparin in 5 per cent dextrose in isotonic solution of sodium chloride was started intravenously. The preheparin clotting time (Lee White venous method) was two and a half minutes. Within four hours after the administration of 200 mg. of heparin (22,000 units), the clotting time was eight minutes.

On October 6 the child appeared almost moribund. Shallow, rapid respirations developed and he became cyanotic. Examination of the chest revealed evidence of metastatic pulmonary suppuration. He was placed in an oxygen tent and given constant intravenous fluids. Both eyes were completely shut, and bilateral proptosis was present. There was pronounced frontal edema. Shortly after administration of heparin was begun, free bleeding began to occur from the lesion on the forehead. The dosage of sulfathiazole was increased to 4 grains (0.26 Gm.) per pound in twenty-four hours and maintained by the use of sodium sulfathiazole by the intravenous in addition to the oral route.

In spite of this high intake, the highest blood level obtainable for sulfathiazole was 4 mg. per hundred cubic centimeters. On October 8, in spite of a clotting time of twelve and one-half minutes obtained by the total administration of 600 mg. of heparin within three days, with constant free bleeding from the wound, the child became steadily worse. The temperature curve remained septic, and the boy was in a comatose state.

Through the kindness of Dr. Paul Hamilton it was possible for us to start the administration of penicillin on October 8.

Administration of sulfathiazole and heparin was discontinued, and 100,000 Oxford units of penicillin was given intravenously in a 5 per cent solution of dextrose within the first twelve hours. There was an apparent dramatic response to penicillin, with an immediate drop in temperature to 103 F. Within twenty-four hours the child began to improve. The septic temperature curve ceased immediately after the administration of penicillin. Within seven days of penicillin therapy, the child became afebrile. During this time the only treatment consisted of administration of penicillin and several transfusions of blood and of serum for supportive reasons. The dosage of penicillin was approximately 100,000 units per day for the first three days, with progressively smaller doses for a total of fourteen days. A total dose of 975,000 Oxford units was given.

On October 15, in spite of striking clinical improvement, with diminution of proptosis, the blood on culture still yielded hemolytic Staph. aureus. In spite of the normal temperature, sulfadiazine was started by mouth. On October 20 the blood was sterile on culture. The only unusual reaction noted to penicillin was a generalized urticaria, which appeared on October 14 and lasted two days. On October 13 a left foot drop was noted.

Ophthalmoscopic consultation by Dr. Robert Hare on October 19 revealed subsiding bilateral proptosis, dilated superficial veins, ptosis of the left upper lid, total left external ophthalmoplegia, partial right external ophthalmoplegia, pallor of both

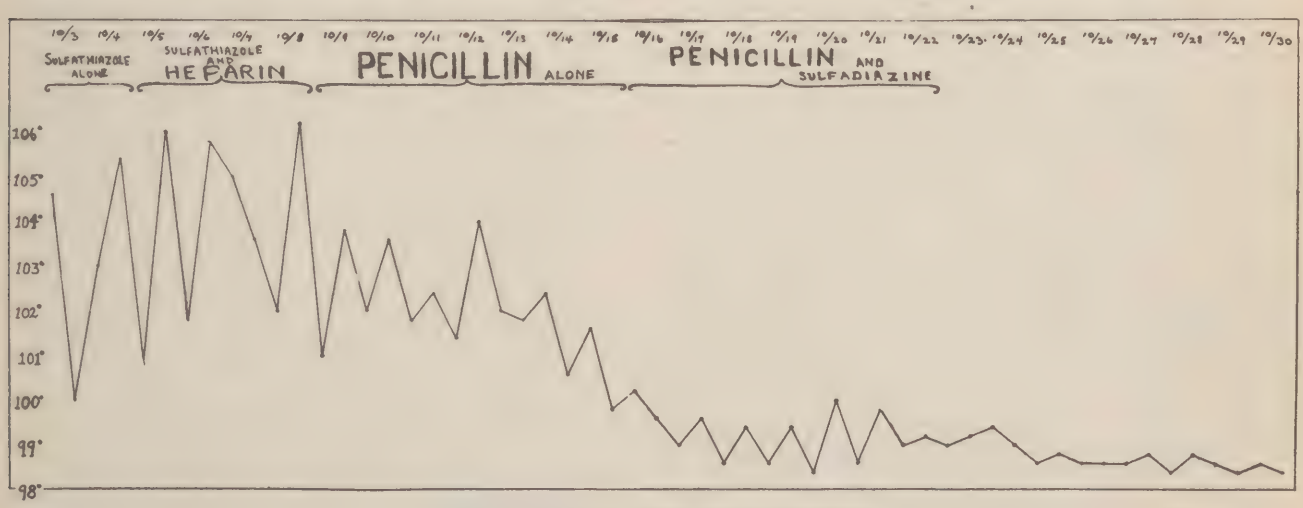

Fig. 2.—Temperature during period of treatment.

disks, bilateral macular edema and bilateral engorgement of the retinal veins. Dr. Hare concluded that the ocular conditions represented the end results of cavernous sinus thrombosis. There was apparently no vision at all in the left eye, but the patient was able to distinguish objects with the right eye at a distance of 2 feet.

Within ten days of penicillin therapy the frontal edema disappeared completely and the furuncle healed. On November 2 the patient was discharged, in excellent general physical condition with the exception of left foot drop, complete ptosis of the left upper lid, bilateral external ophthalmoplegia and early bilateral atrophy of the optic nerve.

The patient has been followed in the clinic, and when last seen, on Jan. 7, 1944, the left ptosis had disappeared completely and the right eye had almost perfect muscle function. The right disk was normal, and the left disk showed much less pallor.

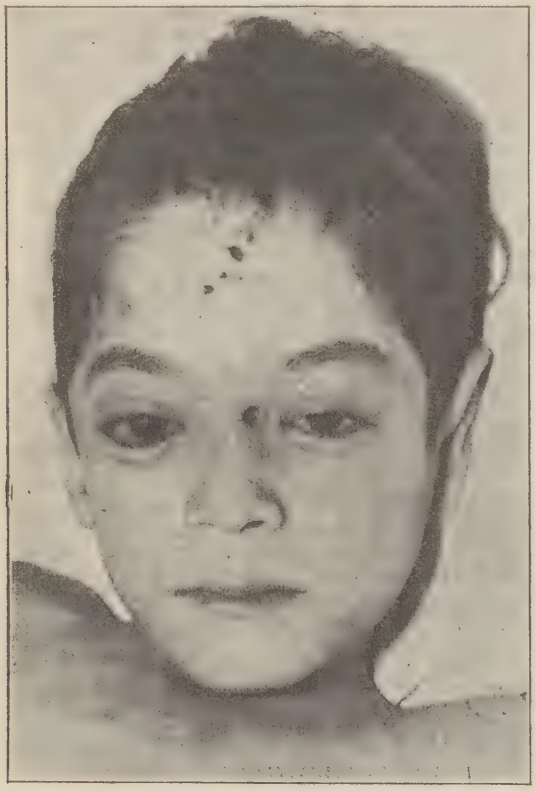

Fig. 3.—Five days after treatment with penicillin.

COMMENT

1. It was quite likely from a clinical standpoint that we were dealing with thrombophlebitis of (*a*) the cavernous sinuses and (*b*) the frontal veins, with possible involvement of the cranial diploic veins, as well as the sagittal (superior longitudinal) sinus.

2. Large doses of heparin (sufficient to decrease the clotting time from two and a half to twelve and a half minutes as well as to reduce the hemoglobin content from 82 to 48 per cent) were of no avail when used for seven days with large doses of sulfathiazole (4 grains per pound in twenty-four hours).

3. The administration of penicillin intravenously was followed within twelve hours by a drop in temperature and by a clinical response.

4. At the time of writing, three months later, the patient is well except for partial ophthalmoplegia and optic neuritis.

SUMMARY

A 5 year old child was cured of bilateral cavernous sinus thrombophlebitis. Recovery followed the administration of penicillin intravenously after preliminary treatment with heparin and sulfathiazole had been of no avail.

676 South Westlake Avenue.

THE USE OF SULFATED OIL AS A SKIN CLEANSER IN THE MANAGEMENT OF ACNE VULGARIS

JACOB H. SWARTZ, M.D., AND IRVIN H. BLANK, PH.D.
BOSTON

It is unlikely that any one single factor is the cause of acne vulgaris. It is quite apparent, however, that there is almost always an overactivity of the sebaceous glands, which produces an increase in the amount of oily secretion on the surface of the skin of most patients. A well accepted principle in the treatment of acne vulgaris is the regular and relatively complete removal of this oily secretion from the cutaneous surface.

During recent years, various cleansing agents other than soap have been used for cleansing the skin. The sulfated oils [1] have been used primarily in the management of cutaneous diseases for which soap is contraindicated.[2] The term sulfated oil applies to any oil, fat, fatty acid or wax of animal or vegetable origin which has been "solubilized" by treatment with concentrated sulfuric acid. The sulfated oils mix well with both oil and water. They are efficient emulsifying agents, and it is thought that they cleanse the skin by means of emulsifying the oils on the cutaneous surface so that these oils can then be easily removed by rinsing with water. This cleansing is accomplished without the formation of lather.

TABLE 1.—*Types of Acne Vulgaris*

Lesions	Type of Acne Vulgaris
Oily and "muddy" complexion	Juvenile
Comedones	Juvenile
Milia	Juvenile
Few papulopustules	Juvenile
Many papulopustules	Papulopustular
Few scars	Papulopustular
Sebaceous cysts	Indurated
Many scars	Indurated

In a discussion of a paper by Lane and Blank [3] on the use of sulfated oil as a detergent in a dermatologic ward, at the 64th annual meeting of the American Dermatological Association in 1941, Dr. McCarthy and one of us (J. H. S.) each stated that he had used the sulfated oils for cleansing the skin of patients with acne vulgaris. During the past four years we have prescribed a detergent containing 25 per cent sulfated oil, 25 per cent mineral oil and 50 per cent water [4] to over 400 patients with acne vulgaris in private practice and also to many clinic patients. Since the purpose of recommending sulfated oil is to bring about better cleansing of the skin, and since the sulfated oil is used in a different way than is soap, each patient should be told just how the sulfated oil should be used. We usually recommend that a small amount of the sulfated oil be poured into the palm of the left hand and then thoroughly rubbed over the unmoistened skin of the face with the fingers of the right hand in the same manner as when applying a cleansing cream. This "massaging" of the face with the oil should be carried on for from one to several minutes and be followed by thorough rinsing with warm water. Since the sulfated oils are completely miscible with water, they will be removed by the water and will carry with them the natural oil on the cutaneous surface, cosmetics and dirt. At the outset it is suggested that the skin be cleansed in this manner three times daily. The frequency of cleansing may be decreased as the skin becomes less oily. The patients

easily adjust themselves to the use of a cleansing agent which does not lather, if they are told in advance not to expect a lather.

A sulfated oil is not a single chemical compound. Its composition will depend on the type of oil which has been sulfated and the method used to prepare the oil. In general the sulfated oils have been found to be nonirritating detergents, but it appears that, with certain processes of manufacture,

TABLE 2.—*Lotion for Patients with Light Complexion*

	Gm. or Cc.
Calamine	4.0
Zinc oxide	8.0
Phenol	2.0
Glycerin	8.0
Spirit of camphor	4.0
Distilled water	ad 240.0

by-products of sulfation may be formed and these by-products may irritate the skin. Up to the present time we have seen no patient with acne vulgaris in whom the sulfated oil has caused a dermatitis of the face.

It is important to differentiate the sulfated oils from the sulfur soaps that have been used in the treatment of acne vulgaris. There is little or no free sulfur in the sulfated oils. The sulfur is chemically combined in the form of the sulfate group and cannot act as free sulfur. So far as can now be determined, the sulfated oil acts solely as a cleansing agent. When the action of sulfur is desired in the treatment of acne vulgaris, it is used in some other form of therapy. The choice of therapy will depend on the type of acne vulgaris being treated.

Acne vulgaris may be subdivided into three types, depending on the nature of the lesions, as is shown in table 1.

For all three types of acne vulgaris the following is recommended: (1) thorough cleansing with sulfated oil three times daily followed by the application of borated alcohol each time, (2) mechanical removal of comedones and (3) a diet. The cleansing technic has been described. The borated alcohol is prepared by mixing equal parts of saturated aqueous boric acid solution and 70 per cent ethyl alcohol. The patient is shown how to remove the comedones with a comedo extractor which has been sterilized by boiling. The patient should be instructed to remove comedones twice a week. Thorough cleansing with the sulfated oil and the application of borated alcohol should precede comedo removal, and the borated alcohol should also be applied after removal. Chocolate, nuts and cooked fats are eliminated from the patient's diet.

With this therapy the juvenile type of acne vulgaris usually shows a satisfactory response. Fewer comedones seem to form, and those which do form are sometimes removed by the cleansing alone.

For the papulopustular type of acne vulgaris, ultraviolet irradiation and the nightly use of a shake lotion are often added to the aforementioned therapy. For patients who have light complexions or for those whose skin is not very oily, the lotion given in table 2 is prescribed.

For patients who have a dark complexion and for those whose skin is quite oily, a more "drying" lotion is prescribed (table 3).

This type of acne vulgaris seems to respond more satisfactorily to a combination of the shake lotion and the sulfated oil cleansing than to a combination of the same shake lotion and soap cleansing.

Roentgen therapy is most frequently used for the indurated

TABLE 3.—*"Drying" Lotion*

	Gm. or Cc.
Calamine	2.0
Zinc oxide	4.0
Phenol	1.0
Spirit of camphor	8.0
Precipitated sulfur	8.0
Alcohol	120.0
Distilled water	ad 240.0

type of acne vulgaris and especially when response to other types of therapy has been slow. Patients are always cautioned against the use of sulfur shake lotions and other irritating preparations when roentgen therapy is being used. Following roentgen therapy, sulfated oil cleansing and the lotion mentioned in table 2 are recommended.

Endocrine therapy is rarely used and only for those patients who seem to present some definite indication of an endocrine imbalance.

SUMMARY

Sulfated oils have been used successfully for cleansing the skin of patients with acne vulgaris.

In the juvenile type of acne vulgaris, such a cleansing method is usually sufficiently "drying" so that shake lotions are unnecessary. Borated alcohol may be used. A diet which eliminates chocolate, nuts and cooked fats is recommended. The patient is shown the correct method for the removal of comedones.

In the papulopustular type of acne vulgaris, shake lotions and ultraviolet therapy are also used.

For the indurated type of acne vulgaris, roentgen therapy is suggested, particularly if response to other types of therapy has been poor.

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1. Formerly referred to as "sulfonated oils."
2. Lane, C. G., and Blank, I. H.: Sulfonated Oil as a Detergent for Diseases of the Skin, Arch. Dermat. & Syph. **43**: 435-443 (March) 1941.
3. Lane, C. G., and Blank, I. H.: Sulfonated Oil as a Detergent: Its Use in a Dermatologic Ward, Arch. Dermat. & Syph. **44**: 999-1008 (Dec.) 1941
4. This preparation is known as Acidolate.

Clinical Notes, Suggestions and New Instruments

AMEBIC ABSCESS OF THE LIVER WITH SECONDARY INFECTION

LOCAL TREATMENT WITH PENICILLIN

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Associate Professor of Medicine and Assistant Professor of Surgery, Respectively, Wayne University College of Medicine
DETROIT

Amebic abscesses of the liver may be divided into two groups from the standpoints of therapy and prognosis. The first group is composed of those without secondary bacterial infection. The accepted method of therapy in this group is the administration of emetine hydrochloride, usually combined with aspiration of the abscess. Open drainage is contraindicated, since it causes a higher fatality rate, chiefly because of the unavoidable postoperative bacterial invasion of the abscess. In a collected series of 5,000 cases, Ochsner and DeBakey[1] report a fatality rate of 5.6 per cent for the cases treated by the closed method and 43.1 per cent for the cases treated by open drainage.

The second group consists of amebic abscesses which have become secondarily infected with bacteria of various types. In these cases the prognosis is much worse, and the accepted surgical treatment is essentially the same as for other pyogenic hepatic abscesses, namely open drainage performed preferably through an extraserous approach. Because of the higher fatality rates associated with open drainage, it has been suggested that some of these infected abscesses might possibly respond to aspiration combined with sulfonamide therapy. Alport and Ghalioungui[2] report a case of what was presumably an amebic abscess of the liver secondarily infected by Bacillus pyocyaneus in which recovery followed repeated aspirations and the local and systemic use of some of the earlier sulfonamide compounds.

The chief point of interest in the present case is the use of penicillin injected into the cavity of an amebic abscess of the liver secondarily infected with beta-hemolytic streptococci of Lancefield group G.

REPORT OF CASE

History.—A Negro aged 41 was admitted to Detroit Receiving Hospital on April 22, 1943 complaining of sharp interscapular pain of twenty-four hours' duration.

The patient had been in good health until the first week of December 1942, when he contracted a "head cold." About one week later he began to cough and noticed a sharp stabbing pain in the lower right side of his chest. He consulted a physician, who told him that he had pleurisy and advised him to stay in bed. The pain became less sharp but persisted as a steady dull ache, which extended downward over the right upper abdominal quadrant. The cough also persisted and was productive of white odorless sputum. During the succeeding months the patient remained ill, confined to his home, and spent most of the time in bed. There was a gradual loss of 18 to 20 pounds (8 to 9 Kg.), mild anorexia, gaseousness and infrequent periods of slight diarrhea alternating with constipation. His general condition improved somewhat by the first of April, and he considered returning to work. His physician advised him, however, to remain at home. About April 15 he began to have night sweats but was unaware of fever or chills. On April 21 a sharp stabbing pain developed in the interscapular area. It was intensified by muscular movements but was not influenced by respiration.

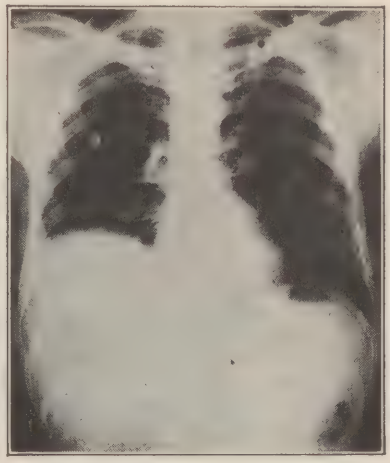

Fig. 1.—Appearance of the chest on Dec. 10, 1938. Note the elevation of the right side of the diaphragm. Compare with figure 2 *A*.

His general health had been good. In 1921 he noticed a sore on his penis but received no treatment for it. In 1926 he was treated for gonorrhea.

In 1938 he was sent to Parkside Hospital in Detroit because his physician suspected that he was suffering from pneumonia. Review of the hospital records reveals that he complained chiefly of pain in his back and in the right side of his chest and abdomen. He had no cough, and the pain in his chest was not pleuritic in type. There were no gastrointestinal complaints. Physical examination of the chest showed only an elevation of the right side of the diaphragm. Except for slight tenderness in the right lumbar region, there were no abnormal abdominal findings. The Kahn reaction of the blood was strongly positive. A roentgenogram of the chest (fig. 1) showed the lungs to be clear, but the dome of the right side of the diaphragm was at the level of the fourth interspace anteriorly. There were no clinical or roentgen findings of atelectasis. The patient's temperature ranged between 98 and 103 F. during the first eight days, then diminished, and was normal after the twelfth day. The tentative diagnosis was syphilis of the liver. The patient received several injections of a bismuth compound but did not recall having taken any antisyphilitic treatment after leaving the hospital.

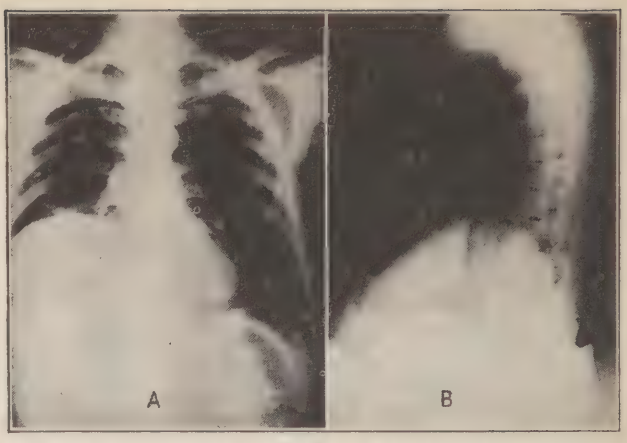

Fig. 2.—Appearance of the chest on May 15, 1943. *A*, anteroposterior and *B*, lateral views showing elevation of the right side of the diaphragm.

In 1940 he was caught between a truck and a coal conveyor and was told that he had sustained an injury of the liver. He was brought to Redford Receiving Hospital, where he remained only overnight. A roentgenogram of the chest showed no fractures of the ribs and the diaphragm in a normal position. His past history by systems was essentially negative except for a three day period of diarrhea in 1939, which he attributed to food eaten in a restaurant. His bowel habits had been normal between that time and the present illness.

The occupational, marital and family histories were noncontributory.

Physical Examination.—The patient was well developed but poorly nourished, was 5 feet 7 inches (170 cm.) in height and weighed 110 pounds (50 Kg.). He appeared chronically ill. His mental state was clear. Examination of the skin, head, eyes, ears, nose, mouth, and throat was essentially negative. There was no cervical or other lymphadenopathy. The thyroid gland was of normal size, and the trachea was in the midline. There were some bulging and lag in expansion of the right lower posterior portion of the thorax but only slight tenderness on compression. Percussion revealed dulness shading into flatness below the 6th rib posteriorly on the right, in the axilla and below the 4th rib in the midclavicular line. Movements of

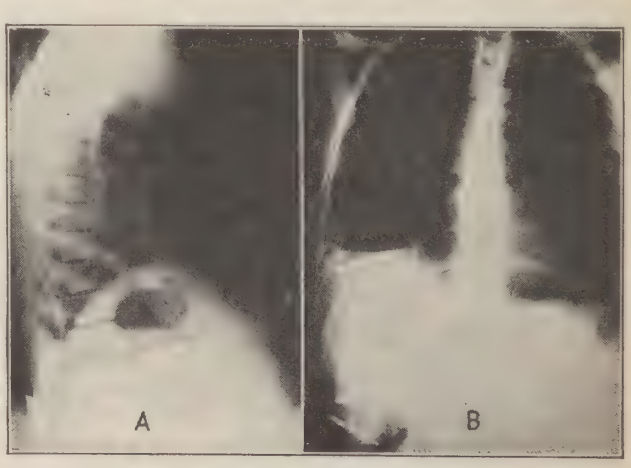

Fig. 3.—*A*, lateral view on May 22, 1943, showing the elevated diaphragm and the abscess cavity in the liver. *B*, anteroposterior view on June 4, showing the ureteral catheter coiled within the abscess cavity.

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From the Departments of Medicine and Surgery of Wayne University College of Medicine and City of Detroit Receiving Hospital.

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2. Alport, A. C., and Ghalioungui, P.: Conservative Treatment of Liver Abscesses, Lancet **2**: 1062-1065 (Nov. 18) 1939.

both sides of the diaphragm were normal as determined by percussion. The breath sounds were absent in the area of impaired resonance and bronchovesicular over a strip just above this. There were occasional crepitant rales. The left lung was clear. The cardiac apical impulse was located in the fifth intercostal space 9 cm. to the left of the midsternal line. Percussion borders were normal. There were no murmurs. The blood pressure was 115/85. Examination of the abdomen revealed tenderness and voluntary muscular rigidity in the right upper quadrant, with an ill defined underlying mass. Evidences of ascites were absent. Rectal examination showed no abnormalities other than a slight enlargement of the prostate gland. The genitalia and the extremities showed nothing remarkable.

Initial Laboratory Studies.—Urinalysis revealed a specific gravity of 1.018, a trace of albumin, no sugar, and 75 leukocytes in each high power field of the centrifuged specimen. The blood contained 3.64 million erythrocytes, and the value for hemoglobin was 5.7 Gm. There were 23,100 leukocytes with the following differential count: neutrophils 74 per cent, of which 46 were filamented and 28 nonfilamented forms; lymphocytes 24 per cent; monocytes 2 per cent. The icterus index was 5.0 and the blood urea 26 mg. per hundred cubic centimeters. The Kline reaction of the blood was negative, as was the blood culture. The value for serum albumin was 2.2 Gm. and that for serum globulin 5.1 Gm. per hundred cubic centimeters. Ingestion of 6.0 Gm. of sodium benzoate resulted in the excretion of only 0.72 Gm. of hippuric acid (expressed as sodium benzoate) in the urine during a period of four hours. The stool was described as soft and brown and gave a strongly positive reaction for occult blood. The sputum contained no tubercle bacilli on repeated tests.

Clinical Course.—During the first three weeks the patient's temperature varied between 99 and 101 F., with a corresponding elevation in pulse rate. He did not appear acutely ill. However, diarrhea became more pronounced than at any previous time, consisting of two to four soft, unformed, brown stools daily. The abdominal tenderness gradually subsided, and the edge of the liver could be defined about 10 centimeters below the right costal margin. Roentgenograms showed elevation of the right side of the diaphragm (fig. 2*A* and *B*). Fluoroscopy revealed normal motion of both sides of the diaphragm.

The combined physical and roentgen findings suggested the diagnosis of hepatic abscess. Stool examinations for parasites were ordered because amebiasis was suspected. After three negative tests, trophozoites of Endamoeba histolytica were found on May 12 and again on May 13. On the latter date and for the ten following days 1 grain (0.06 Gm.) of emetine hydrochloride was injected subcutaneously each day. Additional treatment for the severe diffuse hepatic damage included a diet high in carbohydrate and protein and low in fat and containing generous amounts of brewers' yeast, thiamine hydrochloride, nicotinic acid, halibut liver oil and ascorbic acid. The patient was also given intravenous infusions of dextrose. After three days of this therapy the diarrhea stopped and the thoracic pain disappeared. The patient's temperature decreased to between 99 and 100 F. and his appetite improved. However, serial roentgenograms showed no change in the size of the liver, and the hippuric acid test on May 18 was unchanged.

On May 22 the abscess was aspirated. Procaine hydrochloride was injected into the skin and subcutaneous tissues at the right costal margin in the midclavicular line. A small incision was made in the skin and a 13 gage needle inserted. It was directed upward and posteriorly for a distance of about 4 inches. At this point considerable resistance was encountered. Additional pressure, however, sufficed to force the needle into the abscess cavity, from which 350 cc. of thick gray pus was obtained. Smears showed no amebas but many leukocytes and streptococci, both graded quantitatively as 4+. When grown on blood agar the streptococcus exhibited beta hemolysis. Serologic grouping [3] revealed that it belonged to group G of Lancefield. Figure 3*A* is a lateral view taken just after aspiration of the abscess cavity.

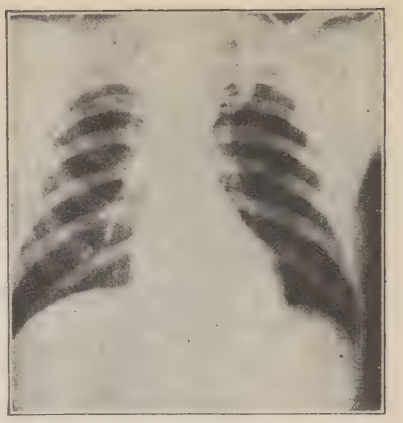

Fig. 4.—Appearance of the chest on September 13, showing the return of the right side of the diaphragm to its normal position.

Because of the evidence of pronounced hepatic damage which would have made open drainage most hazardous, we decided to inject penicillin [4] into the cavity of the abscess. To accomplish this a 13 gage needle was reinserted and a small ureteral catheter passed through the needle. Then the needle was withdrawn and the catheter left in place. A roentgenogram was taken to check the position of the catheter (fig. 3*B*). Five cc. of isotonic solution of sodium chloride, each containing 5,000 Oxford units of penicillin, was injected into the abscess on the evening of May 22. This process was repeated every four hours until eight doses had been given. The amount of penicillin was then reduced to 10,000 units every four hours. This schedule was maintained for seven days, when the dose was further decreased to 5,000 units every four hours. Seven days later, on June 9, penicillin treatment was stopped. The patient received a total of 830,000 Oxford units during a period of fifteen and one-half days.

On May 25, three days after penicillin was started, a smear of the aspirated material showed leukocytes graded as 4+ but no organisms. Cultures yielded no growth. Subsequent cultures on May 27, May 28, June 2 and June 4 were likewise sterile.

Following aspiration of the abscess and treatment with penicillin the patient became afebrile and asymptomatic. On May 27 the value for the hippuric acid test increased slightly to 0.976 Gm., and the levels for serum albumin and globulin increased to 2.8 and 5.46 Gm. per hundred cubic centimeters respectively. The liver gradually decreased in size, as noted on roentgenographic and physical examination. Except to obtain small amounts of pus for cultures, no further aspirations of the abscess were necessary. Motile amebas reappeared in the stools on July 1. Accordingly, 1 grain of emetine hydrochloride was again given subcutaneously each day for five days and was followed by the oral administration of 12 grains (0.8 Gm.) of chiniofon three times daily for twelve days. At the end of this therapy no amebas were found in the stools, but another specimen on July 22 contained an occasional cyst. Sigmoidoscopy revealed no ulceration of the rectum or of the sigmoid portion of the colon. About this time also the level of serum albumin had increased to 3.5 Gm., while that of globulin had decreased to 3.7 Gm. The value for the hippuric acid test had increased to 1.3 Gm., the erythrocytes

3. The serologic grouping of the hemolytic streptococcus was done by Miss Miriam Miller under the direction of Dr. Ivan C. Hall in the Central Laboratory of the Contaminated Wound Project of the Subcommittee on Surgical Infections of the National Research Council, financed by a contract between the Office of Scientific Research and Development and Columbia University.

to 4,190,000 and the hemoglobin to 10.5 Gm. The patient had gained 29 pounds (13 Kg.).

He was discharged from the hospital on July 26 and has been followed in the outpatient department. He has continued on his diet with its vitamin supplements and recently has been taking vioform. On September 15 examination of the chest was entirely negative, but the edge of the liver, which felt slightly firm, was palpable 5 cm. below the right costal margin. The spleen was not palpable. The value for the hippuric acid test had dropped to 0.707 Gm. The serum albumin and globulin levels were each 3.7 Gm., and the bromsulphalein test following intravenous injection of 5 mg. of the dye for each kilogram of body weight showed 60 per cent retention at 5 minutes, a trace at ½ hour and no retention at 60 minutes. Anteroposterior and lateral roentgenograms of the chest were within normal limits (fig. 4).

COMMENT

This case illustrates the value of roentgenography in the diagnosis of amebic abscess of the liver. The patient's chief complaints were related to the thorax, and the history of occasional periods of diarrhea was obtained only after repeated questionings. The physical findings on admission were equivocal, and if it had not been for the roentgenogram which clearly localized the disease of the liver there might have been delay in arriving at the correct diagnosis. The roentgenograms (fig. 2 *A* and *B*) are very similar to those published by Ochsner and DeBakey [1] except that in our case the typical obliteration of the anterior costophrenic angle was absent. Furthermore, the diaphragmatic movements as observed fluoroscopically were not noticeably decreased. The latter finding seemed to favor the diagnosis of hepatic abscess rather than an abscess in the subdiaphragmatic space, which would certainly have immobilized the diaphragm. However, it is reported that diaphragmatic movement is frequently impaired in amebic abscesses of the liver. It is noteworthy that in Ochsner and DeBakey's [1] cases a correct roentgenographic diagnosis was made in 88 per cent.

Another remarkable feature of this case is the clinical and roentgenographic evidence that, in all probability, an amebic infection of the liver was present in December 1938, four years preceding the onset of the symptoms of the present illness. This process, whether a diffuse amebic hepatitis or an actual amebic abscess, had at least partially subsided, as shown by the normal position of the diaphragm in the roentgenogram taken in 1940. If this was the actual course of events, the duration of the disease was unusually long, for among 113 cases classified by Ochsner and DeBakey as chronic amebic abscesses the average duration of symptoms was three to six months and the longest duration three years.

The final point of interest is the consideration of the value of penicillin therapy in this case and its possible value in other cases of secondarily infected amebic abscesses of the liver. The high fatality rate usually associated with open drainage has been mentioned. It should be stated, however, that Ochsner and DeBakey [1] succeeded in reducing this fatality rate to only 6.6 per cent in a group of 15 cases in which extraserous drainage was employed. Even this figure could perhaps be further reduced if operation could be avoided. The use of sulfonamide compounds in 1 reported case also has been mentioned. One might predict that, while sulfonamide therapy would tend to prevent the spread of secondary pyogenic infection throughout the liver, it would not be expected to sterilize the abscess itself, since its action, as in empyema thoracis, is greatly interfered with by the presence of pus. The action of penicillin, on the other hand, is not altered by the presence of pus,[5] as indicated by experimental evidences and its successful clinical use in empyema thoracis and other deep suppurative processes. Therefore one might expect that it would have a favorable effect, particularly when used locally.

It is impossible to judge the value of penicillin in the treatment of secondarily infected amebic abscesses of the liver merely from the results in this 1 case. The practically complete absence of fever or symptoms after a few days of therapy with emetine would seem to indicate that either the streptococcus was of low virulence or that the thick abscess wall minimized the systemic reaction to the infection. However, the organisms were present in very large numbers. While most severe infections in human beings due to beta-hemolytic streptococci are caused by group A organisms, other Lancefield groups may cause infections at times.

Group G beta-hemolytic streptococci were at first thought to be rarely if ever associated with severe human infections,[6] but more recently they have been reported as the causative organisms in such diseases as recurrent lymphangitis and septicemia,[7] puerperal fever with and without septicemia,[8] fatal acute bacterial endocarditis [9] and 2 cases of subacute bacterial endocarditis.[10] They have been isolated also from the human respiratory tract [11] and other human clinical sources,[12] including the feces. In many of the latter sources they have produced only mild infections or were not pathogenic at all. In the present case penicillin caused the rapid destruction of these streptococci, whatever their effect might have been on the clinical outcome.

A trial of aspiration combined with injections of penicillin for the purpose of avoiding open drainage would seem to be desirable in other cases of this kind. Recent studies [13] indicate that the dosage of penicillin used in this case was probably unnecessarily large. Thus in the treatment of empyema thoracis it is recommended that 30,000 or 40,000 units be injected once or twice daily. It is probable also that, while in the present case it seemed unnecessary to aspirate material from the abscess cavity repeatedly, other cases might be benefited by this additional procedure. Such aspirations should not be repeated too frequently, however, since it requires at least six or eight hours for penicillin to exert its maximum effect. For the same reason the use of penicillin as an irrigating solution would be illogical.

The results in this case have been encouraging. It is hoped that those who have similar cases will employ this method of treatment in order to determine whether it will be possible to avoid open drainage in secondarily infected amebic abscesses of the liver.

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4. The penicillin was made available by Dr. Chester S. Keefer, consultant to the Committee on Medical Research, under a contract between the Office of Scientific Research and Development and the Massachusetts Memorial Hospitals.

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19 TWO CASES OF CLOSTRIDIUM WELCHI INFECTION TREATED WITH PENICILLIN

MAXWELL KEPL, M.D.; ALTON OCHSNER, M.D., AND J. LEONARD DIXON, M.D., NEW ORLEANS

We believe that the development of gas gangrene in a traumatic wound depends on four factors: (1) contamination of the wound with soil or foreign bodies containing clostridia, (2) inadequate blood supply to the affected part, (3) inadequate débridement and (4) conditions in the wound for anaerobic growth. A combination of these four factors in a given patient will almost invariably give rise to clinical "gas gangrene."

Once clinical "gas gangrene" has fully developed, the only known treatment is radical surgery, laying the affected parts wide open and many times, of necessity, doing a high guillotine amputation in order to save the patient's life.

Any chemical or biotic substance which will inhibit the growth of clostridia in traumatic wounds would be of inestimable value in saving limbs and lives.

The discovery by Fleming [1] of the action of penicillin and its use by McIntosh and Selbie [2] in experimental Clostridium welchi infections held promise that this drug would be of value in such infections. As animal experiments are inconclusive in regard to human therapy, it remains for the clinician to put penicillin to the final test in regard to its efficacy in the treatment of gas gangrene. The recent report of Keefer, Blake, Marshall, Lockwood and Wood [3] indicates that more clinical observation on the action of penicillin in "gas gangrene" infection is needed in human cases before definite conclusions can be drawn. Lyons [4] also makes a similar plea.

McKnight, Loewenberg and Wright [5] have reported their experience in a case of "gas gangrene." They could not control the "gas gangrene" infection with wide incisions, sulfathiazole systemically, large doses of gas antitoxin and high voltage x-ray therapy. A high arm amputation was resorted to, but gas bubbles persisted in the axillary wound. Intravenous sodium penicillin in isotonic solution of sodium chloride was given continuously on the second postoperative day until the edematous condition of the patient made it necessary to stop therapy. In addition, the patient received 40,000 units directly intramuscularly into the stump. During the next week the temperature gradually dropped, and the wound cleaned up. No positive bacteriologic identification of the causative organism was done, owing to inadequate laboratory facilities. It was agreed by four experienced clinicians, however, that the case was one of clinical "gas gangrene."

Recently we have had occasion to study two cases of Clostridium welchi infection, both of which were treated with penicillin. In one, following a shotgun injury to the lateral aspect of the thigh, there was no evidence of clinical "gas gangrene," but a persistent Cl. welchi cellulitis associated with Staphylococcus aurantiacus, coagulase positive, and a gram negative anaerobic bacillus, unidentified as yet. Calcium penicillin was applied directly to the wound in a dilution of 5 cc. of isotonic solution of sodium chloride containing 20,000 units. Local administration of this dosage was continued for six days. Cultures were taken before, during and after penicillin therapy. Under local penicillin therapy the number of gram negative organisms and Staphylococcus aurantiacus appeared reduced in direct smear preparation with an increase in the number of cocci phagocytized. The clostridia found lacked a good capsule but persisted undiminished in the wound throughout penicillin therapy. A milk tube inoculated with a swab consistently showed "stormy" fermentation. The wound healed slowly by granulation over a period of seven weeks, and at no time was the patient's general condition impaired by the Cl. welchi cellulitis.

The second case was that of a man whose arm was lacerated by broken glass which severed the biceps, the brachialis, the radiobrachialis muscles, the brachial artery, the radial and median nerves and the median basilic vein. Bleeding was severe,

Fig. 1.—Arm and forearm, edematous, "wet" and ischemic before penicillin and surgery. Note the multiple bullae.

and a tight tourniquet was put on before he entered the hospital. Complete débridement and closure were done early, followed by repeated stellate blocks and packing of the injured extremity in ice. The temperature, 100 F. on admission, went to 102 F. the next day. The fingertips were inspected at that time and found warm and pink. The patient began to complain of severe pain in the arm. On the third day the arm was swollen and painful to the touch. Dressing on the fourth day revealed crepitation along the radial side of the forearm, with bubbles of gas escaping from the suture line. There was bronzing of the tissues around the elbow and a putrefactive odor to the arm. Multiple bullae were present on the skin of the forearm. The fingertips were cold and pale (fig. 1). The patient was toxic and in great pain, with a temperature of 103 F.

All sutures were removed, smears of exudate made and a blood culture was taken. Cl. welchi and beta-hemolytic streptococci were identified from the wound, and blood culture was positive for beta-hemolytic streptococci. Sulfadiazine was immediately given by mouth, 70,000 units of "gas gangrene antitoxin" given intramuscularly, hot wet dressings applied locally, and a transfusion of 500 cc. of citrated blood administered. The next morning the temperature had dropped a little, he appeared less toxic, and his blood culture had become negative. His arm had definitely become worse, however, and the edema appeared to have spread to the axilla, while crepitation could be noticed in the upper arm and shoulder. One hundred thousand units of sodium penicillin was given in 100 cc. of isotonic solution of sodium chloride intravenously, 500 cc. of citrated blood was given and a guillotine amputation was done under cyclopropane anesthesia. At operation, the skin and fascia of the stump were split longitudinally and left open. Swabs taken from this area at operation showed gram positive bacilli and gram positive cocci, which on culture proved to be Cl. welchi and beta-hemolytic streptococci.

Leah Seidman Shaffer, ScD., made the bacteriologic studies.

From the Department of Surgery, School of Medicine, Tulane University.

Dr. Kepl is fellow in orthopedic surgery, Division of Medical Sciences, National Research Council.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Tulane University of Louisiana.

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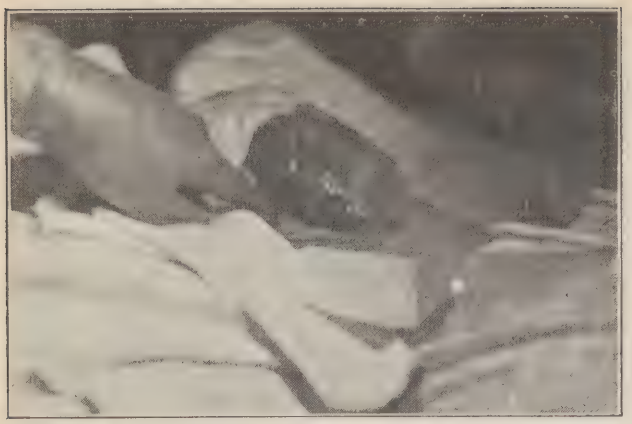

Fig. 2.—Appearance of stump the day after surgery and penicillin. The gloved finger is placed in the lateral skin flap. The exposed biceps muscle is viable.

Powdered calcium penicillin, 100,000 units, was sprinkled dry into the stump, Dakin tubes were inserted, the stump was bandaged and sealed with cellophane, and a continuous local drip of 1,000 cc. of isotonic solution of sodium chloride containing 100,000 units of calcium penicillin started.

The next morning the wound was dressed. The exposed muscle was clean. A culture taken from the wound showed only a scant growth of diphtheroid organisms. No Cl. welchi or beta-hemolytic streptococci were found (fig. 2) on smea or culture.

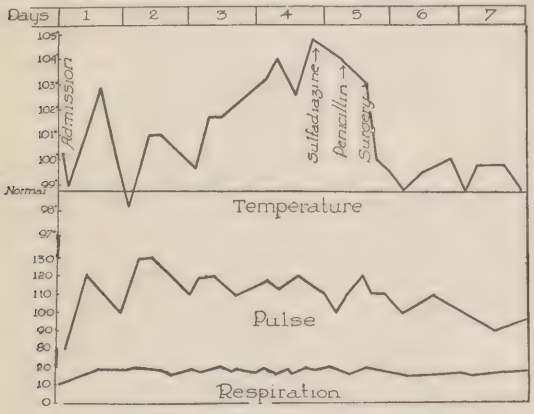

Fig. 3.—Temperature, pulse and respiration during the first week in the hospital. Notice the sharp drop in temperature and pulse rate following penicillin and amputation.

The clinical course postoperatively was uneventful except that a thrombophlebitis developed at the site of the intravenous penicillin therapy. The stump now has a pyocyaneus infection from ward contamination, but healing is assured. The patient still has a low fever, 99 F., but the stump is ready for skin grafting. Figure 3 shows the temperature, pulse and respiration curves during the first week in the hospital.

SUMMARY

Of 2 cases of Cl. welchi infection, 1 was treated locally with calcium penicillin and the other systemically with sodium penicillin and locally with calcium penicillin. Careful bacteriologic studies showed persistence of Cl. welchi in the case of cellulitis treated with calcium penicillin locally, while the use of penicillin systemically and locally, combined with guillotine amputation, caused the disappearance of beta-hemolytic streptococcus and Cl. welchi from the spreading infection. After oral sulfadiazine, beta-hemolytic streptococci could not be recovered from the blood stream. It must be emphasized that good surgery was the deciding factor in the second case and that penicillin is of most benefit when used in conjunction with good surgical principles.

A PRIMIPARA WITH DIABETES AND MILD TOXEMIA TREATED SUCCESSFULLY WITH DIETHYL STILBESTROL

Byron D. Bowen, M.D., Buffalo

The wide experience of Priscilla White[1] in the study of the chorionic gonadotropic hormones and the effect of the use of the estrogens and progesterone in the treatment of pregnant diabetic patients, on whom an increase of these hormones was found, is more than suggestive that their use reduces the incidence of, and is effective in, the treatment of preeclamptic toxemia of pregnancy and thereby reduces the fetal and maternal mortality.

The nature of this action is not understood, nor is the metabolism of the estrogens. It may be that the estrogenic substances have a "salutary" effect on the liver. It has been demonstrated that pregnant women can tolerate large amounts of estrogens. Among the possibilities of this beneficial effect are the inhibition of the diabetogenic hormones of the pituitary, the reduction of the rate of glycogenolysis or the removal of antagonistic insulin action, as White's cases have shown that insulin could usually be reduced after the administration of the estrogen. The following case demonstrates this relationship to a high degree:

REPORT OF CASE

History.—Mrs. E. F., aged 23, admitted to the diabetic service of the Buffalo General Hospital Oct. 7, 1943 and discharged Jan. 9, 1944, was referred by Dr. Raymond May, Alden, N. Y. The diabetes was discovered in 1932; she had taken insulin since that time. Because of considerable variation in weight and insulin dosage it was suspected that the control of the diabetes had not been accurate much of this time. She had been in various hospitals on several occasions for adjustment of the diabetic regimen. One of these admissions, at the age of 15, was because of diabetic coma. She had had an enlargement of the thyroid gland since the age of 10. At the time of admission the insulin dose was 90 units of the protamine zinc and 10 to 20 units of the unmodified before breakfast. Her last menstrual period was March 17, 1943. Since the onset of the pregnancy she had experienced some loss of appetite, headache and periods of weakness. For several weeks before admission she had rather frequent attacks of what she thought were insulin reactions—palpitation, sweating, shortness of breath and a choking sensation.

Physical examination showed the following positive findings: diffuse but slight enlargement of the entire thyroid gland; slight accentuation of the basal heart sounds, especially on the aortic side; blood pressure 118 systolic, 82 diastolic; pulse rate 120 to 130; seven months' pregnancy. She was on the whole cheerful, but there appeared to be quite violent mood swings, when she became quite depressed.

Course.—Shortly after admission she began to have attacks of "insulin reactions"; blood sugar determinations made during these attacks were always elevated, and orange juice failed to relieve them quickly. These "spells" were always associated with tachycardia, and during one attack her pulse rate rose to 180. Two electrocardiograms taken two and five days after admission showed a normal sinus rhythm with a rate of 116 and 138 respectively, negative T_3 and a tendency to right axis deviation. It then came to our attention, from the Social Service Department, that her husband, who had been in the armed forces, was missing several months. It seemed probable that these alleged "insulin reactions" were, in all probability, anxiety attacks. She was seen in consultation by Dr. Mabel Ross from the Psychiatric Department, who concurred in the nature of the attacks. However, Dr. Ross believed that the patient's failure to accept the diabetes and her inability to live as other people did was also a contributing factor. No further attacks occurred after their nature was carefully explained to the

patient and she had been assured that she would get along all right. On October 15, one week after admission, slight pretibial edema was first noted. There was no essential change in the blood pressure. The urine continued to be free of albumin and abnormal elements in the sediment.

On November 1 she had her first attack of diarrhea. These attacks continued several times each week—often as many as eight watery evacuations daily. These disappeared with the other evidences of toxemia. Several stools showed no occult blood. Culture of the feces was negative for pathogenic enteric organisms.

On November 23 the first trace of albumin in the urine was reported. This persisted and reached a 2 plus reaction by December 8.

On November 4 her blood pressure, which had been measured twice daily, showed its first conspicuous rise: 144 systolic, 84 diastolic; it continued to be essentially in that zone save for an occasional normal or rare higher reading until the toxemia improved.

On admission her red blood cells numbered 4,100,000, with 13.5 Gm. of hemoglobin per hundred cubic centimeters of blood. The white cells numbered 11,000, with 8 per cent bands, 56 filaments, 2 eosinophils, 30 lymphocytes and 4 monocytes. A slight anemia was first noted on November 18, when the red cells dropped to 3,500,000, with 9 Gm. of hemoglobin per hundred cubic centimeters. The leukocytes dropped to 7,900 per cubic millimeter, with no essential change in the differential. On November 26 the red blood cells numbered 3,660,000, with 11 Gm. of hemoglobin.

Two of our enterprising and interested clinical clerks, Mr. Melvin N. Wood and Mr. Paul J. Wolfgruber, determined the serum chorionic gonadotropic hormones on November 11. They were found to be at least 500 rat units per hundred cubic centimeters of blood. This was repeated again on November 26. Then one rat, which had a dose of serum corresponding to 1,700 rat units per hundred cubic centimeters, showed a corpus luteum, but the other rat, which received an amount corresponding to 1,000 rat units per hundred cubic centimeters of blood, showed no corpora lutea macroscopically. Just before her delivery an attempt was made to estimate the blood serum chorionic gonadotropic hormones. Unfortunately this was indeterminate.

On December 1 the patient was given diethylstilbestrol 2 mg. three times a day in the hope that it would alleviate the toxemia. Her weight, which had steadily increased from 58 Kg. (127½ pounds) on admission, had by this time reached 67 Kg. (147½ pounds). Coincident with the use of the diethylstilbestrol there was a prompt and gradual loss of weight with conspicuous diuresis, so that the weight was reduced to 62 Kg. (137 pounds) by the time of delivery on December 17. Also the systolic blood pressures were definitely lower, but the diastolic remained in the neighborhood of 90.

From the beginning the diabetes was difficult to manage. Except for the first two weeks, when the carbohydrate content in her diet was changed back and forth several times from 180 Gm. of carbohydrate to 140 Gm., her diet remained constant all through the observations at 160 Gm. of carbohydrate, 80 Gm. of protein and 110 Gm. of fat. A combination of protamine zinc insulin 90 units and unmodified insulin 30 units resulted in continuous glycosuria up to as high as 50 Gm. daily. An equal number of units of the unmodified insulin given in three doses—morning, evening and midnight—gave somewhat better control, but as the toxemia became more apparent this had to be increased gradually until the patient was receiving 90 units before breakfast, 68 before supper and 68 at midnight by December 1, when the diethylstilbestrol was started. The fasting blood sugar on November 29 was 250 mg. per hundred cubic centimeters. Promptly after the administration of diethylstilbestrol, hypoglycemic reactions, which had not been present before, followed—fifteen in eleven days; in three of these, concentrated dextrose solution had to be given intravenously. This occurred in spite of the sharp reduction of the insulin dosage. The reactions did not cease until the dose had been lowered to 44 units in the morning, 30 units before supper and 10 units at midnight. It is interesting that there were but a few grams of dextrose in the urine even after the administration of 50 cc. of 50 per cent dextrose intravenously.

She was delivered on December 17 by Dr. Clyde Randall. Both her labor and her delivery were uneventful. She had an episiotomy. Caudal and chloroform anesthesia were used. Her blood pressure taken during labor was 120 systolic, 80 diastolic on one occasion and 128 systolic, 90 diastolic on another. The weight of the male fetus was 7 pounds 7 ounces (3,570 Gm.).

She required only slightly less insulin after delivery than she had previously: 36 units before breakfast, 16 before supper and 10 units at midnight.

She was discharged on a regimen of 180 Gm. of carbohydrate, 90 Gm. of protein and 120 Gm. of fat with 90 units of protamine zinc insulin and 16 of the unmodified insulin before breakfast. There was slight glycosuria occasionally during the day. Her fasting blood sugar was 182 mg. per hundred cubic centimeters. She had no insulin reactions.

SUMMARY

A primipara who was severely diabetic and who had had diabetes for twelve years was studied in the hospital for a period of three months.

The development of mild toxemia of pregnancy was observed —edema, albuminuria, diarrhea, mild hypertension and anemia. During this period the insulin requirement was nearly doubled. The chorionic gonadotropic hormones exceeded 500 rat units per hundred cubic centimeters of blood.

Soon after the oral administration of diethylstilbestrol 6 mg. daily the symptoms and signs of the toxemia disappeared, and the insulin dosage had to be promptly reduced because of the occurrence of many insulin reactions. At that time an estimation of the chorionic gonadotropic hormone was, unfortunately, indeterminate.

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notes

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1. White, P., and Hunt, H.: Pregnancy Complicating Diabetes: A Report of Clinical Results, J. Clin. Endocrinol. 3: 500 (Sept.) 1943.

PENICILLIN AND SKIN GRAFTING

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DETROIT

Few patients are more miserable than those with large unhealed third degree burns. Early skin grafting of the burned areas is the only means of quickly returning these patients to a useful life. The longer this procedure is delayed, the greater the immediate threat of death and the ultimate development of scars and deformity. The aim of all treatment, therefore, is reepithelization of the burned areas as promptly as possible. In general, it requires from one to three months to achieve this aim. The chief causes for the prolonged healing are (1) the necessity of deferring grafting until the burned tissue has sloughed and the granulating bed is ready to accept a graft, (2) the necessity for multiple grafting operations because of the lack of sufficient donor sites or the inability of the patient to tolerate grafting of the entire burn at one time and (3) the necessity of grafting the same area more than once because previous grafts have partially or completely failed to take.

Harvey and Connor [1] have devised a method of rapidly removing the dead tissue. Ordinarily it requires fifteen to forty days for burned tissue to separate. By shortening this time to a few days they have overcome one of the greatest factors prolonging the convalescence of burned patients. Although lack of donor sites will always remain as a limiting factor, improvements in the care of burned patients have made it possible and will continue to make it possible to graft larger areas at one operation. The necessity of grafting the same area more than once remains, therefore, as the chief factor tending to prolong the convalescence of these patients.

Skin grafts fail to take because of (1) infection, (2) failure to maintain the graft in contact with the recipient site and (3) the lack of adequate blood supply in the recipient site. Any one skilled in the art of skin grafting has at his command the means of maintaining a skin graft in contact with the recipient site and of insuring an adequate blood supply for the graft. However, in spite of the most careful preparation of the granulating bed a certain number of split thickness grafts are partially or completely lost because of infection.

Padgett [2] reported the percentage of takes of a large series of split thickness grafts applied to contaminated and to aseptic recipient sites. The analysis of his results (table 1) shows that infection is the most common cause of partial or complete loss of such a graft.

In approximately one third of the cases in which grafts were placed on contaminated recipient sites, 25 per cent or more of the graft was lost. In only about two thirds of these patients were satisfactory takes obtained in which only 10 per cent or less of the graft was lost. In contrast, satisfactory takes were obtained in 98 per cent of the grafts done on aseptic recipient sites. Furthermore, a review shows that many patients whose first grafts failed also lost large parts of successive grafts. This has been our experience and has usually been due to infection of the granulating bed with sulfonamide resistant Streptococcus haemolyticus or Staphylococcus aureus.

A large denuded area of the body usually becomes infected with Pseudomonas pyocyaneus, Proteus vulgaris, Escherichia coli or other gram negative bacilli of intestinal origin. There is yet no chemotherapeutic agent that will adequately control these organisms. Fortunately, in most cases they seem to act primarily as saprophytes and do not interfere with the growth of split thickness grafts. Many burns, however, become infected with beta hemolytic streptococci, Staphylococcus aureus and other coagulase positive micrococci. It is these organisms that are responsible for the failure of skin to grow when transplanted to granulating surfaces. Although the sulfonamides control many hemolytic streptococcus infections, they are ineffective against the occasional resistant strain and against Staphylococcus aureus and the other coagulase positive micrococci. While their use has improved the results of skin grafting, especially in the presence of susceptible hemolytic streptococci, it has not solved the problem.

TABLE 1.—*Padgett's Results*

Percentage of Graft Lost	Number of Cases	
"Fresh Burns"		
Total grafts	44	
0 - 10	28 (63.6%)	In 31.8% of the cases 21% or more of the graft was lost
11 - 20	2 (4.5%)	
21 - 25	1 (2.3%)	
26 - 40	1 (2.3%)	
41 - 100	12 (27.2%)	
Grafts on Other Obviously Contaminated Recipient Sites		
Total grafts	17	
0 - 10	9 (52.9%)	In 35.3% of the cases 21% or more of the graft was lost
11 - 20	2 (11.8%)	
21 - 30	2 (11.8%)	
31 - 100	4 (23.5%)	
Grafts on Aseptic Recipient Sites		
Total grafts	151	
0 - 10	148 (98%)	In only 2% of the cases 11% or more of the graft was lost
11 - 25	2 (1.4%)	
26 - 100	1 (0.6%)	

Penicillin is an extremely powerful bacteriostatic and bactericidal agent that has the advantage of acting not only against Streptococcus haemolyticus but also against Staphylococcus aureus. It seemed important, therefore, to determine whether its administration at the time of skin grafting would improve the percentage of takes.

Nineteen split thickness grafts were performed on 17 patients who were receiving penicillin intramuscularly. In general, grafting was done as soon as the slough had separated, usually three to four weeks after the burn had occurred. In 5 instances, however, grafting was delayed because of (1) the slow separation of a deep slough, (2) the necessity for multiple operations or (3) the admission of patients to our hospital some time after they had been burned. The initial dressings consisted of a wide variety of substances, zinc oxide ointment, glass cloth and cellucotton, zinc

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The work described in this paper was done, under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Wayne University.

1. Harvey, S. C., and Connor, G. J.: The Healing of Deep Thermal Burns, read before the American Surgical Association, Chicago, May 3, 1944.

2. Padgett, E. C.: Skin Grafting, Springfield, Ill., Charles C Thomas, Publisher, 1942.

TABLE 2.—*Details of Treatment*

Patient	Age	Days Elapsing Between Injury and Grafting	Location	Size of Graft	Cultures Before Grafting	Cultures at First Dressing	Dosage of Penicillin	Percentage of Take
A. T.	33	28	Shoulder and arm	65 sq. in.	M. aurantiacus coagulase —; diphtheroids	M. aurantiacus coagulase —; diphtheroids; gram + cocci	10,000 units every 2 hours for 5 doses before grafting 10,000 units every 2 hours for 5 days after grafting	100%
J. B.	52	..	Foot	30 sq. in.	Ps. pyocyaneus; diphtheroids	M. aurantiacus coagulase —; M. epidermidis coagulase —; B. coli; diphtheroids	None before grafting 5,000 units every hour for 5 days after grafting	100%
M. M.	30	30	Thighs	35 sq. in.	M. aurantiacus coagulase —; Ps. pyocyaneus; diphtheroids	M. epidermidis coagulase —; M. aurantiacus coagulase +; Ps. pyocyaneus; diphtheroids; aerobic gram + rods	5,000 units every hour for 12 doses before grafting 5,000 units every hour for 5 days after grafting	95%
W. C.	52	66	Leg and foot	90 sq. in.	M. varians coagulase +; Ps. pyocyaneus; Ps. fluorescens; aerobic gram + rods	Gram + rods; Ps. fluorescens; Ps. pyocyaneus	5,000 units every hour for 18 hours before grafting 5,000 units every hour for 5 days after grafting	100%
B. P.	40	25	Shoulders and scalp	54 sq. in.	M. varians coagulase +; Ps. fluorescens; M. tetragenes; aerobic gram + rod	M. varians coagulase +; Ps. fluorescens; diphtheroids	10,000 units every hour for 18 hours before grafting 10,000 units every hour for 4 days after grafting	95%
I. S.	5	20	Back and chest	50 sq. in.	M. aurantiacus coagulase +; beta hemolytic streptococcus; B. coli; diphtheroids; B. alkaligenes	Ps. pyocyaneus; diphtheroids; M. epidermidis coagulase +	5,000 units every hour for 24 hours before grafting 5,000 units every hour for 4 days after grafting	95%
C. H.	10	180	Chest, axilla and arm	125 sq. in.	M. varians coagulase +; gram + rod; gram neg. rod; M. aurantiacus coagulase +; M. epidermidis coagulase —	M. varians coagulase +; diphtheroids	5,000 units every hour for 5 days before grafting —95% 5,000 units every hour for 9 days after grafting	(This loss was due to hematoma beneath graft)
D. T.	3	20	Chest and abdomen	30 sq. in.	M. aurantiacus coagulase +; M. varians coagulase +; diphtheroids; gram neg. rods	M. aurantiacus coagulase +; diphtheroids; B. coli; B. aerogenes	None before grafting 5,000 units every hour for 2 days after grafting, then 2,500 units every hour for 3 days after grafting	100%
B. M.	5	60	Knee	50 sq. in.	Ps. pyocyaneus; M. epidermidis coagulase —	Ps. pyocyaneus; diphtheroids; M. epidermidis coagulase +	5,000 units every hour for 18 hours before grafting 5,000 units every hour for 2 days after grafting, then 2,500 units every hour for 3 days after grafting	95%
R. B.	5	40	Arms and shoulders	42 sq. in.	M. aurantiacus coagulase +; Ps. pyocyaneus	M. aurantiacus coagulase +; Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 4 days after grafting	90%
B. M.	38	30	Leg	16 sq. in.	M. aurantiacus coagulase +; M. epidermidis coagulase —; Ps. pyocyaneus; aerobic gram + rod	Beta hemolytic streptococcus; Ps. pyocyaneus; M. epidermidis coagulase —	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 4 days after grafting	95%
C. W.	1	19	Chest	30 sq. in.	M. varians coagulase +; B. coli; beta hemolytic streptococcus; aerobic gram + rod	Ps. pyocyaneus; gram + rod	1,000 units every hour for 12 hours before grafting 1,000 units every hour for 5 days after grafting	95%
L. W.	19	25	Trunk	135 sq. in.	Ps. pyocyaneus	Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	90%
L. W.	10	44	Trunk	30 sq. in.	Ps. pyocyaneus; Proteus vulgaris	Ps. pyocyaneus; Proteus vulgaris	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	100%
R. M.	43	25	Thigh	60 sq. in.	M. varians coagulase +; Proteus vulgaris; Ps. pyocyaneus	Proteus vulgaris; Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	80%
J. V.	52	28	Hand	28 sq. in.	Ps. pyocyaneus; M. aurantiacus coagulase +; M. varians coagulase +; B. aerogenes	M. aurantiacus coagulase —; Ps. pyocyaneus; B. aerogenes; aerobic gram + rod	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	100%
G. R.	10	25	Thighs	160 sq. in.	Proteus vulgaris; beta hemolytic streptococcus; Staph. aureus	Proteus vulgaris; Beta hemolytic streptococcus; Staph. aureus	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	90%
G. R.	10	43	Leg	72 sq. in	Proteus vulgaris; Ps. pyocyaneus	Proteus vulgaris; Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 10,000 units every 2 hours for 5 days after grafting	85-90%
J. C.	46	25	Arm and hand	64 sq. in.	M. varians coagulase +; M. aurantiacus coagulase +; B. coli	None	5,000 units every hour for 24 hours before grafting 5,000 units every hour for 24 hours after grafting	100%

peroxide in a carbowax base, and several other experimental ointments. The dressings were changed at intervals of five to fourteen days, depending on the patient's condition and the requirements of certain studies that were in progress on these patients. In only 2 instances were wet dressings employed. At the time of grafting the dressings were removed in the operating room, and the exudate was washed away with warm isotonic solution of sodium chloride. If the granulations were excessive they were cut away; otherwise the grafts, which were cut with the Padgett dermatome, were placed directly on the granulating bed and held in place with fine silk sutures. A single layer of fine mesh gauze impregnated with zinc oxide ointment was placed next to the graft. This was covered with a few layers of ordinary gauze, and the entire area was then covered with mechanics' waste and wrapped with elastic bandage. The initial dressing was changed on the fourth, fifth or sixth day.

All the patients received penicillin intramuscularly. The dose and the duration of therapy varied somewhat from patient to patient. In general, therapy was started about twelve hours before operation and was continued until the time of the first dressing. The exact details of therapy are given in table 2. With one exception, from 90 to 100 per cent of the transplanted skin took in every instance. The exception occurred in an uncooperative alcoholic addict who had third degree burns of the perineum, both thighs and legs. Only 80 per cent of the grafts placed on his groin and thighs took. The loss in this case was probably due to failure of the dressings to hold the grafts in place.

The loss in all cases occurred at the margin of the grafts where they overlapped the new epithelium growing in from the margins of the burned area. This thin layer of new epithelium prevents the graft from taking, and, unlike normal skin, it is not strong enough to survive when covered with a graft. The result is a slough of both the new epithelium and the margin of the graft. If the new epithelium is cut away and the graft joined to normal skin, this marginal loss does not occur.

The administration of penicillin did not seem to alter the bacterial flora a great deal; cultures taken at the time of the first dressing from the margins of the grafts and from the sutures usually yielded the same organisms that were present on the granulating surface before grafting. In spite of their persistence, they did not seem to affect the growth of the graft. Penicillin, therefore, must hold them in check until the skin has a chance to become established in its new bed.

Though penicillin has been administered to only 17 patients at the time of skin grafting, we believe that its use has the following definite advantages:

1. It permits early grafting. Split thickness grafts can be successfully applied as soon as the slough has separated without further time consuming preparation of the granulating area.
2. It appears to prevent the loss of skin from infection that ordinarily occurs in about one third of the cases in which split thickness grafts are placed on contaminated recipient sites.

Before penicillin was available, we performed over a hundred grafts in patients with third degree burns. Although many excellent takes were obtained, in about one third of the cases 25 per cent or more of the graft was lost because of the occurrence of infection. Therefore the consistency with which excellent takes were obtained in this series of 19 grafts has been very impressive to us. We are presenting the method with the hope that others will try it.

notes

venereal diseases

PENICILLIN TREATMENT OF EARLY SYPHILIS: II

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In a preliminary report[1] the influence of penicillin therapy on the clinical manifestations and serologic reactions of patients with early syphilis was presented. The report was based on the results of a curtailed period of observation of a group of 4 patients. It is our purpose in the present paper to record the findings of post-treatment observation of the original group for periods in excess of three hundred days. It is also desired to record certain items of information which have resulted from the treatment of an additional 100 patients.

REVIEW OF ORIGINAL GROUP

Of the group of 4 patients the records of whom formed the basis for the preliminary report,[1] all have been maintained under observation. It will be recalled that these patients displayed dark field positive lesions of early syphilis at the time of treatment. The therapy consisted of an intramuscular injection of 25,000 units of penicillin administered at four hour intervals for forty-eight injections. The total amount of the product utilized was 1,200,000 units and the total time of therapy was about eight days. No other antisyphilitic medication has been employed. The post-treatment observation has consisted of a clinical and serologic examination at weekly intervals for the first six months and monthly observations thereafter. A spinal fluid examination was carried out at the completion of six months post-treatment observation.

Three members of the original group experienced a rapid healing of penile ulcerations and attained seronegativity within the initial three months of observation. These patients have remained clinically and serologically negative up to the present. The remaining patient has displayed circumstances which warrant discussion.

In this patient the penile lesion healed promptly and the serologic tests were recorded as negative on the 71st day. This situation maintained until the 286th day of observation, at which time strongly positive reactions were recorded in all test procedures. At that time the patient was under treatment for specific urethritis in a distant clinic. After some delay the patient was again made available for study and was found to have a single ulcerative lesion, on an indurated base, located on the inner surface of the lower lip. The regional lymph glands were enlarged and firm. There was no other evidence of involvement of skin or mucous membranes or of general adenopathy. Dark field examination of secretions secured from the lesion, after all precautions had been taken to avoid the contamination of the specimen by mouth spirochetes, was considered to be positive for Treponema pallidum.

Although this patient is being classed as a treatment failure, the probability of reinfection is inescapable. Retreatment with penicillin has been carried out.

Table 1 shows the serologic record of the first patient treated with penicillin for early syphilis. Table 2 shows the complete serologic record of patient 4, including serologic relapse or serologic upstroke accompanying reinfection.

In continuing the general study a series of approximately 100 patients have been treated in essentially the same manner as was employed in the original group. Although the post-treatment period of observation has not been of sufficient duration in a large enough group to warrant the drawing of conclusions, some interesting observations may be presented at this time. These are presented as informative material only and with the understanding that they may or may not be substantiated by more complete data.

The principal clinical features of the study may be summarized in the following manner:

The therapy has consisted of an intramuscular injection of 20,000 units of penicillin administered at three hour intervals, night and day, for sixty injections. The total amount of penicillin employed was 1,200,000 units. No other antisyphilitic medication has been used. All patients have been managed in a uniform manner, and it has not been necessary to decrease dosage or abandon the therapy in any instance. With three exceptions (acute arsenical intoxications) all the patients have displayed lesions characteristic of early syphilis (primary and/or secondary).

Herxheimer-like reactions, or therapeutic shock, of varying degrees of severity were observed during the first day of treatment in 86 patients. Ulcerations and cutaneous lesions manifested a tendency toward prompt recession. All uncomplicated ulcers were completely epithelized at the time of completion of treatment. No severe toxic reactions have been encountered. There were 2 instances of exfoliative dermatitis, 1 mild in character and of short duration, the second more severe and requiring about three weeks for return to normal. The two patients had been treated with the same manufacturer's lot of material. As other irritative qualities were attributed to this particular product, the possibility of impurities being accountable for the skin reaction is present.

Because of the rapid disappearance of lesions the main reliance in evaluating the therapy has been placed on the serologic tests. On the reasonable assumption

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Read in a panel discussion on "Penicillin in the Treatment of Syphilis" before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

1. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**: 355-357 (Dec.) 1943.

that the trend of the serologic reactions may be considered as an index to the progress of early syphilis in the human being, the treated patients may be placed into several rather well defined groupings. For a consideration of this phase the records of patients who have had in excess of seventy-five days satisfactory follow-up observation have been selected for scrutiny.

It may be well to state that the serologic routine which has been utilized in this study represents as complete a coverage as is practical: a total of seven accredited methods representing supersensitive and diagnostic flocculation methods, one diagnostic complement fixation technic and three methods with which the reagin content of each positive blood specimen has been quantitated.

On the basis of an arbitrary minimum of seventy-five days of satisfactory post-treatment observation, the records of 52 patients become available for scrutiny. The average duration of observation is one hundred and thirty-five days.

TABLE 1.—*Results of Serologic Tests in Case 1*

Duration of Disease, Nine Days

Time After Start of Therapy	Qualitative Methods							Quantitative Methods		
	Supersensitive Kline Exclusion	Diagnostic Flocculation					Complement Fixation, Kolmer Simplified	Diagnostic Flocculation		Complement Fixation, Kolmer
		Mazzini	Kline Diagnostic	Kahn Standard	Hinton	Eagle		Mazzini	Kahn	
Days										
0	..	4	..	4	Pos	Pos	4	4 4 4 2 1 -	4 4 4 2 ± -	4 4 4 4 4 1
1	..	4	..	4	Pos	Pos	4	4 4 4 2 1 -	4 4 4 2 ± -	4 4 4 4 4 3
9	4	4	4	4	Pos	Pos	4	4 4 4 4 2 -	4 4 4 4 1 -	4 4 4 4 2 -
23	..	4	..	3	Pos	Pos	4	4 3 2 - - -	4 4 1 - - -	4 4 4 3 ± -
30	4	4	3	3	Pos	—	4	4 4 4 2 - -	4 4 3 1 - -	4 4 4 2 ± -
37	4	4	1 Dbt	3	Dbt	—	3	4 4 2 1 - -	4 1 - - - -	3 3 2 ± - -
44	3	4	—	1 Dbt	—	—	4	4 3 2 - - -	4 ± - - - -	4 4 3 ± - -
51	1 Dbt	4	—	—	—	—	4	4 2 - - - -	1 - - - - -	4 4 4 1 ± -
58	1 Dbt	4	—	—	—	—	—	4 3 - - - -	1 - - - - -	- - - - - -
65	2	2 Dbt	—	—	—	—	—	2 1 - - - -	- - - - - -	- - - - - -
72	1 Dbt	2 Dbt	—	—	—	—	—	2 1 - - - -	- - - - - -	- - - - - -
80	—	2 Dbt	—	—	—	—	—	2 ± - - - -	± - - - - -	- - - - - -
86	—	2 Dbt	—	—	—	—	—	2 - - - - -	- - - - - -	- - - - - -
93	—	1 Dbt	—	—	—	—	—	1 - - - - -		
Months										
4	—	—	—	—	—	—	—			
5	—	—	—	—	—	—	—			
6	—	1 Dbt	—	—	—	—	—			
7	—	—	—	—	—	—	—			
8	—	—	—	—	—	—	—			
9	—	—	—	—	—	—	—			
11	—	1 Dbt	—	—	—	—	—			

TABLE 2.—*Results of Serologic Tests in Case 4*

Duration of Disease, Eight Days

Time After Start of Therapy	Qualitative Methods							Quantitative Methods		
	Supersensitive Kline Exclusion	Diagnostic Flocculation					Complement Fixation, Kolmer Simplified	Diagnostic Flocculation		Complement Fixation, Kolmer
		Mazzini	Kline Diagnostic	Kahn Standard	Hinton	Eagle		Mazzini	Kahn	
Days										
0	..	1 Dbt	..	—	—	—	—	- - - - - - - -	- - - - - - - -	- - - - - - - -
1	4	4	± Dbt	1 Dbt	—	Pos	—	2 1 - - - - - -	3 ± - - - - - -	± ± ± - - - - -
8	..	4	..	3	—	Pos	4	3 2 - - - - - -	4 4 ± - - - - -	4 4 4 2 ± - - -
15	4	4	1 Dbt	3	Pos	Pos	± Dbt	4 3 2 1 - - - -	4 3 1 - - - - -	± ± ± ± - - - -
22	4	3	± Dbt	3	Pos	Dbt	± Dbt	3 1 - - - - - -	4 1 ± - - - - -	± 1 ± - - - - -
30	1 Dbt	2 Dbt	± Dbt	—	Dbt	—	± Dbt	2 1 - - - - - -	1 - - - - - - -	± ± 1 ± - - - -
36	± Dbt	2 Dbt	—	—	—	—	—	2 - - - - - - -	± - - - - - - -	- - ± ± - - -
43	—	2 Dbt	—	—	—	—	—	2 1 - - - - - -	± - - - - - - -	- - - - - - - -
50	± Dbt	1 Dbt	—	—	—	—	—	1 - - - - - - -	- - - - - - - -	- - - - - - - -
57	—	1 Dbt	—	—	—	—	—	1 - - - - - - -	± - - - - - - -	- - - - - - - -
64	± Dbt	1 Dbt	—	—	—	—	—	1 - - - - - - -	- - - - - - - -	- - - - - - - -
71	—	—	—	—	—	—	—	- - - - - - - -	- - - - - - - -	- - - - - - - -
86	—	—	—	—	—	—	—	- - - - - - - -	- - - - - - - -	- - - - - - - -
93	—	—	—	—	—	—	—	- - - - - - - -	- - - - - - - -	- - - - - - - -
Months										
4	—	—	—	—	—	—	—			
5	—	—	—	—	—	—	—			
6	± Dbt	—	—	—	..	—	—			
7	—	1 Dbt	—	—	..	—	—			
8	—	—	—	—	..	..	—			
Days										
286	4	4	2	4	..	..	4			4 4 4 ± - - - - -
295	4	4	4	4	..	Pos	4	4 4 4 2 1 - - - -	4 4 1 ± - - - - -	4 4 4 4 1 - - - -
318	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	4 4 4 4 4 3 - - -	4 4 4 4 4 4 ± - -
326	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 3 1 -	4 4 4 4 4 4 1 - -	4 4 4 4 4 4 4 ± -

Of this group of 52 patients, 6 with dark field positive lesions were in the seronegative phase of the disease at the time of treatment and passed through the observation period without positive findings being recorded. The records of 25 additional patients display positive serologic reactions in some or all test methods, with a reversal to negative findings during the observation period. The average time for reversal in this group was seventy days. Thus 31 patients may be considered as having responded in a favorable manner up to the present.

In 7 patients there has been a progressive decline in the serologic titer, and although complete reversal in all tests has not been accomplished there has not been a tendency toward a return of the high titer reactions which were recorded at the time of treatment, and it is anticipated that complete reversal will be accomplished with the passage of time. However, there is no assurance of this contingency. There is the possibility that these patients eventually will be added to the favorably reacting groups.

In an additional group of 7 patients the records display an initial post-treatment trend toward seronegativity with subsequent unmistakable evidence of a return to the high titer reactions. These are considered to be instances of serologic relapse.

The remaining 7 patients have displayed serologic patterns which render difficult the making of a favorable

TABLE 3.—*Results of Serologic Tests in Case 10: Pattern Considered to Be Favorable*

Duration of Disease, Twenty-One Days

Time After Start of Therapy	Qualitative Methods: Supersensitive Kline Exclusion	Qualitative Methods: Diagnostic Flocculation: Mazzini	Qualitative Methods: Diagnostic Flocculation: Kline Diagnostic	Qualitative Methods: Diagnostic Flocculation: Kahn Standard	Qualitative Methods: Diagnostic Flocculation: Hinton	Qualitative Methods: Diagnostic Flocculation: Eagle	Qualitative Methods: Complement Fixation, Kolmer Simplified	Quantitative Methods: Diagnostic Flocculation: Mazzini	Quantitative Methods: Diagnostic Flocculation: Kahn	Quantitative Methods: Complement Fixation, Kolmer
Days										
0	± Dbt	1 Dbt	—	—	Pos	—	—	1 1 1 - - - - - -	- - - - - - - - - -	- - - - - - - - -
1	1 Dbt	3	—	2	Pos	—	—	3 3 2 1 - - - - -	2 ± - - - - - - -	- - - - - - - - -
3	1 Dbt	3	—	2	Pos	Pos	3	3 3 2 1 - - - - -	2 ± - - - - - - -	3 4 4 3 2 ± - - -
8	4	4	4	4	Pos	Pos	4	4 4 3 2 2 1 - - -	4 4 2 1 ± - - - -	4 4 4 4 4 - - - -
14	4	4	4	4	Pos	Pos	4	4 4 4 3 2 - - - -	4 4 2 ± - - - - -	4 4 4 4 3 ± - - -
20	4	4	1 Dbt	4	Pos	Pos	± Dbt	4 4 3 2 1 - - - -	4 3 ± - - - - - -	± ± 1 1 - - - - -
28	2	4	± Dbt	3	Pos	—	± Dbt	4 3 2 1 1 - - - -	4 ± ± - - - - - -	± ± ± ± - - - - -
35	1 Dbt	2 Dbt	± Dbt	1 Dbt	Pos	—	—	2 2 1 1 - - - - -	3 ± - - - - - - -	- - - - - - - - -
42	± Dbt	2 Dbt	—	—	Pos	—	± Dbt	2 1 1 - - - - - -	1 - - - - - - - -	± ± - - - - - - -
48	± Dbt	—	—	—	—	—	—	- - - - - - - - -	- - - - - - - - -	- - - - - - - - -
56	± Dbt	1 Dbt	—	—	—	—	—	1 - - - - - - - -	- - - - - - - - -	- - ± ± ± - - - -
63	—	1 Dbt	—	—	—	—	—	1 - - - - - - - -	- - - - - - - - -	- - - - - - - - -
70	—	1 Dbt	—	—	—	—	—	1 - - - - - - - -	- - - - - - - - -	- - - - - - - - -
77	—	1 Dbt	—	—	—	—	—	1 - - - - - - - -	- - - - - - - - -	- - - - - - - - -
85	—	—	—	—	—	—	—	- - - - - - - - -	- - - - - - - - -	- - - - - - - - -
91	—	—	—	—	—	—	—	- - - - - - - - -	- - - - - - - - -	- - ± ± ± - - - -
Months										
4	—	—	—	—	Dbt	—	—			
5	± Dbt	—	—	—	—	—	—			
6	—	—	—	—	—	—	—			
7	—	—	—	—	—	—	—			

Pattern showing low reading reactions at the beginning of therapy, with an increase in titer during treatment and a rapid reversal to negative.

TABLE 4.—*Results of Serologic Tests in Case 35: High Titer Reactions at Onset of Therapy*

Duration of Disease, Sixty-Nine Days

Time After Start of Therapy	Qualitative Methods: Supersensitive Kline Exclusion	Qualitative Methods: Diagnostic Flocculation: Mazzini	Qualitative Methods: Diagnostic Flocculation: Kline Diagnostic	Qualitative Methods: Diagnostic Flocculation: Kahn Standard	Qualitative Methods: Diagnostic Flocculation: Hinton	Qualitative Methods: Diagnostic Flocculation: Eagle	Qualitative Methods: Complement Fixation, Kolmer Simplified	Quantitative Methods: Diagnostic Flocculation: Mazzini	Quantitative Methods: Diagnostic Flocculation: Kahn	Quantitative Methods: Complement Fixation, Kolmer
Days										
—1	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	3 4 4 4 4 4 1 - -	4 4 4 4 4 4 4 1 -
1	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	4 4 4 4 4 3 ± - -	4 4 4 4 4 4 2 ± -
5	4	4	4	4	Pos	Pos	4	4 4 4 4 4 2 1 - -	4 4 4 4 4 2 - - -	4 4 4 4 4 4 3 ± -
13	4	4	4	4	Pos	Pos	4	4 4 4 4 4 1 - - -	4 4 4 4 4 3 ± - -	4 4 4 4 4 4 2 - -
20	4	4	4	4	Pos	Pos	4	4 4 4 4 3 1 - - -	4 4 4 4 2 1 - - -	4 4 4 4 4 1 ± - -
27	4	4	4	4	..	Pos	4	4 4 4 3 ± - - - -	4 4 3 2 ± - - - -	4 4 4 4 4 1 ± - -
34	4	4	4	4	Pos	Pos	4	4 4 3 2 - - - - -	4 3 2 1 - - - - -	4 4 4 1 - - - - -
41	4	4	2	2	Pos	Pos	4	4 3 2 1 - - - - -	4 3 ± - - - - - -	4 4 4 1 - - - - -
49	4	4	4	2	Pos	Dbt	4	4 2 2 1 - - - - -	4 ± - - - - - - -	4 4 4 ± - - - - -
56	4	3	2	± Dbt	..	—	3	3 2 1 - - - - - -	4 ± - - - - - - -	3 3 1 - - - - - -
63	4	2 Dbt	1 Dbt	± Dbt	—	—	1	2 2 - - - - - - -	2 - - - - - - - -	1 ± - - - - - - -
69	3	2 Dbt	1 Dbt	—	—	—	1	2 1 - - - - - - -	1 - - - - - - - -	1 ± - - - - - - -
91	1 Dbt	1 Dbt	—	—	—	—	—			
99	2	1 Dbt	—	—	Dbt	—	—			
112	1 Dbt	1 Dbt	—	—	—	—	± Dbt			
119	1 Dbt	1 Dbt	—	—	—	—	± Dbt			
126	± Dbt	—	—	—	—	—	—			
153	± Dbt	—	—	—	—	—	—			

A representative pattern of patients with secondary syphilis. High titer reactions show a consistent and progressive trend toward reversal to negative.

or unfavorable classification at this time. Some pessimism is felt as to the effectiveness of the therapy in this group.

If the patients are grouped in accordance with the stage of the disease at the time of treatment, some items of potential interest become discernible. Of the 52 patients 30 may be classed as having dark field positive primary syphilis. Of this number 1 patient, previously mentioned, developed a clinical relapse nine months following treatment. A second patient displayed a well defined serorelapse after an initial favorable serologic trend for one hundred and twelve days after treatment. An additional member of the group experienced a clinical relapse after eighty-four days of practically unchanged high titer positive serologic reactions. Two patients who have displayed a progressive but protracted trend toward reversal cannot be readily classified at this time. The remaining 25 patients are at this time clinically and serologically negative. Therefore there is a possibility of there being twenty-seven satisfactory responses.

Of the 22 patients who displayed evidence of secondary syphilis and who were well into the seropositive phase of the disease at the time of treatment, 11 have

TABLE 5.—*Results of Serologic Tests in Case 8: Relapse Following Initial Favorable Trend*

Duration of Disease, Forty-Six Days

Time After Start of Therapy	Qualitative Methods: Super-sensitive Kline Exclusion	Qualitative Methods: Diagnostic Flocculation: Mazzini	Qualitative Methods: Diagnostic Flocculation: Kline Diagnostic	Qualitative Methods: Diagnostic Flocculation: Kahn Standard	Qualitative Methods: Diagnostic Flocculation: Hinton	Qualitative Methods: Diagnostic Flocculation: Eagle	Qualitative Methods: Complement Fixation, Kolmer Simplified	Quantitative Methods: Diagnostic Flocculation: Mazzini	Quantitative Methods: Diagnostic Flocculation: Kahn	Quantitative Methods: Complement Fixation, Kolmer
Days										
0	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 3 - -	4 4 4 4 4 4 4 ± -	4 4 4 4 4 4 4 - -
1	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 3 1 -	4 4 4 4 4 4 3 ± -	4 4 4 4 4 4 4 ± -
8	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 3 - -	4 4 4 4 4 4 1 - -	4 4 4 4 4 4 4 3 -
12	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 2 - -	4 4 4 4 4 4 1 - -	4 4 4 4 4 4 1 - -
19	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 - - -	4 4 4 4 4 2 ± - -	4 4 4 4 4 4 2 - -
26	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 - - -	4 4 4 4 2 ± - - -	4 4 4 4 4 3 ± - -
33	4	4	4	4	Dbt	Pos	4	4 4 4 4 4 1 - - -	4 4 4 1 ± - - - -	4 4 4 4 4 ± - - -
40	4	4	4	4	Dbt	Pos	4	4 4 4 4 3 1 - - -	4 4 2 1 - - - - -	4 4 4 4 3 ± - - -
47	4	4	4	4	Dbt	Dbt	4	4 4 4 3 - - - - -	4 4 3 ± - - - - -	4 4 1 ± - - - - -
54	4	3	2	3	Dbt	—	4	3 2 2 2 - - - - -	4 3 1 ± - - - - -	4 4 4 3 1 - - - -
61	4	4	3	3	Dbt	—	4	4 4 4 3 2 - - - -	4 2 ± - - - - - -	4 4 4 4 4 ± - - -
68	4	4	4	3	Pos	—	4	4 4 4 3 2 - - - -	4 2 ± - - - - - -	4 4 4 4 2 ± - - -
75	4	4	4	4	Pos	Pos	4	4 4 4 4 2 - - - -	4 4 4 3 ± - - - -	4 4 4 4 2 ± - - -
82	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	4 4 4 4 4 1 - - -	4 4 4 4 4 ± - - -
90	4	4	4	4	Pos	Pos	4	4 4 4 4 4 2 1 - -	4 4 4 4 2 - - - -	4 4 4 4 4 4 ± - -
96	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 4 2 - -	4 4 4 4 4 4 2 - - -	4 4 4 4 4 4 4 4 3
105	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	4 4 4 4 4 4 2 - - -	4 4 4 4 4 4 - - -
110	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 - - -	4 4 4 4 4 4 ± - -	4 4 4 4 4 4 ± - -
117	4	4	4	4	Pos	Pos	4	4 4 4 4 4 - - - -	4 4 4 4 4 - - - -	4 4 4 4 4 - - - -
124	4	4	4	4	Pos	Pos	4	4 4 4 4 4 1 - - -	4 4 4 3 1 - - - -	4 4 4 4 4 3 - - -
131	4	4	4	4	Pos	Pos	4	4 4 4 4 3 - - - -	4 4 4 2 ± - - - -	4 4 4 4 2 ± - - -
138	4	4	4	4	Pos	Pos	4	4 4 4 4 1 - - - -	4 4 4 4 2 - - - -	4 4 4 4 4 4 1 - -
152	4	4	3	4	Pos	Pos	4	4 2 1 - - - - - -	4 4 3 - - - - - -	4 4 3 ± - - - - -
166	4	2 Dbt	1 Dbt	3	Pos	Pos	4	.....	.....	4 4 1 ± - - - - -
188	4	2 Dbt	4	± Dbt	Pos	Dbt	± Dbt	.....	.....	± ± - - - - - - -
194	4	4	2	—	Dbt	Dbt	4	.....	.....	4 3 - - - - - - -
201	4	4	2	2	Pos	Dbt	4	4 3 2 2 - - - - -	.....	4 3 2 ± - - - - -
208	4	4	3	3	Pos	Pos	4	4 4 3 2 - - - - -	.....	4 4 4 3 ± - - - -

TABLE 6.—*Results of Serologic Tests in Case 68*

Duration of Disease, Thirty Days

Time After Start of Therapy	Qualitative Methods: Super-sensitive Kline Exclusion	Qualitative Methods: Diagnostic Flocculation: Mazzini	Qualitative Methods: Diagnostic Flocculation: Kline Diagnostic	Qualitative Methods: Diagnostic Flocculation: Kahn Standard	Qualitative Methods: Diagnostic Flocculation: Hinton	Qualitative Methods: Diagnostic Flocculation: Eagle	Qualitative Methods: Complement Fixation, Kolmer Simplified	Quantitative Methods: Diagnostic Flocculation: Mazzini	Quantitative Methods: Diagnostic Flocculation: Kahn	Quantitative Methods: Complement Fixation, Kolmer
Days										
0	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 3 1 -	± ± 2 4 2 1 ± - -	4 4 4 4 4 4 4 ± -
1	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 2 - -	2 4 4 4 4 2 - - -	4 4 4 4 4 4 4 ± -
7	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 2 1 -	2 2 2 2 2 2 ± - -	4 4 4 4 4 4 ± - -
11	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 2 - -	2 4 4 4 4 1 ± - -	4 4 4 4 4 4 4 ± -
18	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	± 4 4 3 2 ± - - -	4 4 4 4 4 4 ± - -
25	4	4	2	4	Pos	Pos	4	4 4 4 4 4 4 2 - -	2 4 4 4 3 - - - -	4 4 4 4 4 4 4 ± -
32	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 2 - -	4 4 4 4 4 3 1 - -	4 4 4 4 4 4 3 ± -
39	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 2 - -	2 4 4 4 4 3 ± - -	4 4 4 4 4 4 4 4 ±
46	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	2 4 4 4 2 ± - - -	4 4 4 4 4 4 4 4 ±
53	4	4	4	4	Pos	Pos	4	4 4 4 4 2 1 - - -	± ± ± 1 1 ± ± - -	4 4 4 4 4 4 3 - -
60	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 2 - -	4 4 4 4 2 ± - - -	4 4 4 4 4 4 3 - -
66	4	4	4	4	Pos	Pos	4	4 4 4 4 3 2 1 - -	3 4 4 4 3 ± - - -	4 4 4 4 4 4 ± - -
74	4	4	4	4	Pos	Pos	4	4 4 4 4 4 4 2 - -	3 3 4 4 4 ± - - -	4 4 4 4 4 4 - - -
86	4	4	4	4	Dbt	Pos	4	4 4 4 3 2 - - - -	4 4 4 ± - - - - -	4 4 4 4 4 1 - - -
93	4	4	4	4	..	Pos	4	4 4 4 4 4 3 1 - -	4 4 4 4 3 ± - - -	4 4 4 4 4 4 ± -
109	4	4	4	4	Pos	Pos	4	4 4 4 4 4 3 1 - -	4 4 4 4 4 2 - - -	4 4 4 4 4 4 4 ± -

Pattern displayed by patient with early syphilis in which the therapy failed to influence the serologic picture.

favorable at the moment, displays a protracted decline which presages an unfavorable outcome.

The remaining tables represent serologic patterns which are considered to be representative of groups of patients.

COMMENT

The contrast which is displayed in the groups of treated patients rather indicates that (1) very early infections respond in the most favorable manner and (2) the increase in probable failures in patients with secondary syphilis indicates the need of a more vigorous therapy than that used in this study.

In evaluating the effectiveness of arsenic therapy in syphilis and of sulfonamide therapy in gonorrhea, it has been noted that a certain proportion of individuals fail to experience the same curative response which may be demonstrable in the majority of patients. A similar characteristic seems to be emerging in penicillin therapy of syphilis.

A majority of patients with early syphilis appear to respond to treatment in a satisfactory manner, as judged by the clinical course and the trend of the serologic reactions. A small group in the present series (7 definitely and 2 probably) appear to have derived a minimum of permanent benefit and must be considered as treatment failures.

In sulfonamide therapy of gonorrhea, failures of this type are classed as sulfonamide resistant and much has been written in regard to the drug resistance of strains of Neisseria gonorrhoeae. While accepting as possible that strain characteristics may play a role in determining the effectiveness of a therapy, it is felt that certain host factors are largely responsible for determining whether or not an agent, as penicillin, will be effective in infections which are amenable, as a rule, to treatment. It is felt that one of the most important problems in chemotherapy is a delineation of this essential factor and the development of means through which it may be favorably influenced.

In all the patients who have been classed as failures an observation period in excess of eighty-four days was required before an adverse decision as to treatment status was considered warranted. The data in these instances and in those which may occur among patients treated in the future will be scrutinized in an effort to determine a reliable basis for a more prompt decision predicated on clinical response and serologic pattern.

The making available of a pure or reasonably pure penicillin might effect a distinct change in the treatment picture both as to results produced and as to the duration of treatment, dosage and the interval between injections. Equally important will be the development of an assay method which gives assurance that the spirocheticidal activity of a product is consistently proportional to the antibacterial activity on which the present Oxford unit is based.

CONCLUSION

It is desired to recall that the disease syphilis is one which is characterized by chronicity, with long periods of latency and a distinct tendency to clinical and serologic recurrence. The evaluation of any therapy will require a prolonged trial utilizing a wide variety of treatment schedules and a carefully controlled follow-up system. The combined experience available at this time has served to illuminate only a few of the important aspects. The remainder must await the passage of time.

THE TREATMENT OF EARLY SYPHILIS WITH PENICILLIN

22

A PRELIMINARY REPORT OF 1,418 CASES

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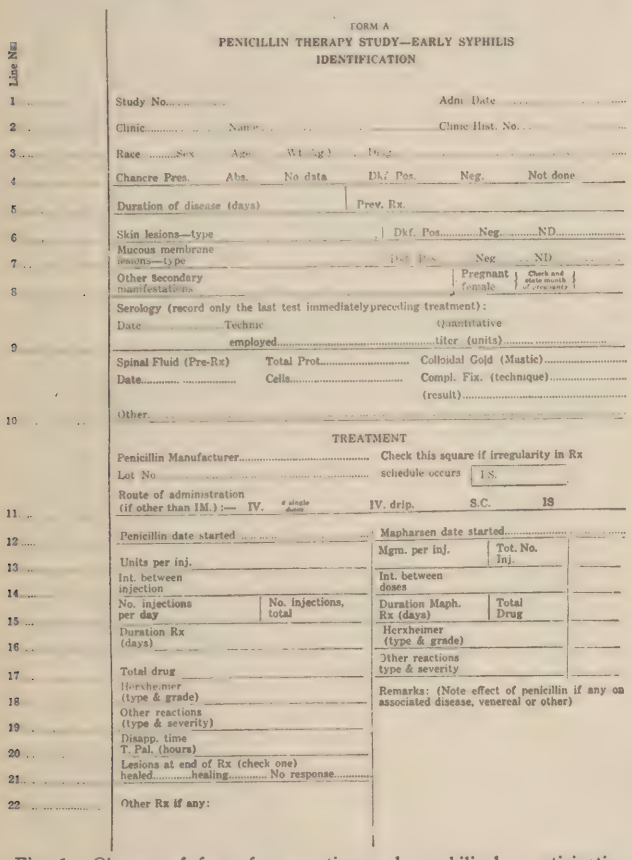
In December 1943 Mahoney, Arnold and Harris [1] reported briefly on the effect of pencillin in experimental syphilis of rabbits and in 4 human patients with seropositive primary syphilis. As a result of these observations and of further experimental studies carried out in the laboratories of Mahoney [2] and Eagle [3] there was organized, about Sept. 1, 1943, under the general auspices of the Committee on Medical Research of the Office of Scientific Research and Development and under the specific direction of the Subcommittee on Venereal Diseases, National Research Council, a cooperative study of the effect of penicillin in syphilis in human beings. A Penicillin Panel was appointed by this subcommittee, with membership including the authors of this paper.[4] Because of the special problems confronting the armed forces, particular emphasis has been laid on early syphilis and on neurosyphilis, though other forms of late syphilis have also been studied. The preliminary results obtained to date are here presented in two papers, this dealing with early syphilis; the other, with Stokes as spokesman for the group, with late syphilis.

The penicillin employed has been derived from Army, Navy, Public Health Service, and Office of Scientific Research and Development sources. Only the sodium salt has been employed in these studies. Penicillin allocated to the Office of Scientific Research and Development for research purposes has been distributed by the Committee on Chemotherapeutic and Other Agents, National Research Council, Dr. Chester Keefer, chairman. This committee has allocated gradually increasing amounts of the drug to the Subcommittee on Venereal Diseases, which in turn has apportioned it among those civilian clinics selected for participation in the study.

Early syphilis is at present under investigation in twenty-three clinics or research centers. These, with the names of the responsible investigators, are as follows: U. S. Army (Fort Bragg, North Carolina, Capt. William Leifer, Camp Howze, Texas, Major Franklin Grauer), U. S. Navy (Naval Medical Center, Bethesda, Md., Lieut. Comdr. E. C. Barksdale), United

States Public Health Service (Marine Hospital, Stapleton, S. I., Dr. J. F. Mahoney), Massachusetts Memorial Hospital, Boston (Dr. Oscar Cox), Bellevue Hospital, New York (Dr. Evan Thomas), Chicago Intensive Treatment Center (Dr. S. W. Becker), Cleveland City Hospital and University Hospitals (Dr. Harold Cole), University of Pennsylvania Hospital (Dr. J. H. Stokes), University of Texas (Dr. Chester Frazier), Washington University, St. Louis (Dr. W. Barry Wood Jr.), Yale University (Dr. Francis Blake), Dallas Venereal Disease Clinic (Dr. Arthur Schoch), Leland Stanford Jr. University Hospital (Dr. C. W. Barnett), Duke University Hospital (Dr. C. L. Calloway), Vanderbilt University Hospital (Dr. R. H. Kampmeier), Johns Hopkins Hospital (Drs. J. E.



FORM A

PENICILLIN THERAPY STUDY—EARLY SYPHILIS

IDENTIFICATION

Line No.

1 Study No. ... Adm. Date ...

2 Clinic ... Name ... Clinic Hist. No. ...

3 Race ... Sex ... Age ... Wt. (kg.) ... Diag. ...

4 Chancre Pres. ... Abs. ... No data ... Dk. Fld. Pos. ... Neg. ... Not done ...

5 Duration of disease (days) ... Prev. Rx. ...

6 Skin lesions—type ... Dk. Fld. Pos. ... Neg. ... ND ...

7 Mucous membrane lesions—type ... Dk. Fld. Pos. ... Neg. ... ND ...

8 Other Secondary manifestations ... Pregnant / Female ... Check and state month of pregnancy

Serology (record only the last test immediately preceding treatment):

9 Date ... Technic employed ... Quantitative titer (units) ...

Spinal Fluid (Pre-Rx) Total Prot. ... Colloidal Gold (Mastic) ...

Date ... Cells ... Compl. Fix. (technique) ... (result) ...

10 Other ...

TREATMENT

Penicillin Manufacturer ... Check this square if irregularity in Rx schedule occurs ... I.S.

Lot No. ...

Route of administration (if other than IM.):— IV. (single dose) IV. drip. S.C. IS

11 Penicillin date started ... Mapharsen date started ...

12 Units per inj. ... Mgm. per inj. ... Tot. No. Inj. ...

13 Int. between injection ... Int. between doses ...

14 No. injections per day ... No. injections, total ... Duration Maph. Rx (days) ... Total Drug ...

15 Duration Rx (days) ... Herxheimer (type & grade) ...

16 Total drug ... Other reactions type & severity ...

17 Herxheimer (type & grade) ... Remarks: (Note effect of penicillin if any on associated disease, venereal or other)

18 Other reactions (type & severity) ...

19 Disapp. time T. Pal. (hours) ...

20 Lesions at end of Rx (check one) healed ... healing ... No response ...

21 Other Rx if any:

22

Fig. 1.—Obverse of form for reporting early syphilis by participating clinics.

Moore and C. F. Mohr), Tulane University (Dr. R. V. Platou), Presbyterian Hospital, New York (Dr. A. B. Cannon), University of Virginia Hospital (Dr. D. C. Smith), New York Hospital (Dr. Walsh McDermott) and the Detroit Health Department (Dr. Loren Shaffer). This report is based on the work of these investigators and of many of their associates and assistants, too numerous to name.[5]

These clinics and centers agreed (1) to treat patients with early syphilis on assigned treatment schedules in an effort to define as promptly as possible the all important time-dose relationship and (2) to pool their results under the Penicillin Panel of the Subcommittee on Venereal Diseases. Only those patients in whom the diagnosis of early syphilis was indubitable, on the basis of actual demonstration of treponemes, were to be acceptable. All patients were to be originally examined and subsequently followed in as nearly as possible a uniform manner. The immediate results of treatment were to be reported to the Penicillin Panel on specially devised forms (figs. 1 and 2), susceptible of coding, punch carding and machine statistical analysis.

TABLE 1.—*Four Treatment Schedules*

Duration of Treatment	Interval Between Injections	Route of Administration	Single Dose	No. of Injections	Total Dose
7½ days	3 hours	Intramuscular	1,000 units	60	60,000 units
7½ days	3 hours	Intramuscular	5,000 units	60	300,000 units
7½ days	3 hours	Intramuscular	10,000 units	60	600,000 units
7½ days	3 hours	Intramuscular	20,000 units	60	1,200,000 units

On the basis of the very preliminary studies of Mahoney and his associates, there appeared to be five variables requiring study. These were (1) the route of administration, originally chosen [1] as intramuscular for the sake of slightly delayed absorption and excretion as compared to the intravenous route; (2) the interval between injections, at first selected [1] as every three hours day and night on the basis of known data as to the rate of absorption and excretion; (3) the duration of treatment, originally arbitrarily selected as eight days; [1] (4) the total dosage, again arbitrarily selected as 1,200,000 units,[1] and (5) possible combinations of penicillin with other drugs, e. g. mapharsen.

At the outset it was decided by the Penicillin Panel to hold the first three of these variables constant; i. e., all cases were to be treated by the intramuscular route every three hours day and night to a total of sixty injections given in seven and one-half days. The first effort was to be to define the minimum effective dose so given within this time period. Four treatment schedules were accordingly drawn up (table 1).

These covered a twenty fold dosage range up to and including the original maximum arbitrarily chosen by Mahoney and his co-workers. In addition there were originally planned (but subsequently temporarily dropped) two other groups, to test the combined effect of penicillin plus mapharsen. These two groups comprised a total penicillin dosage of 60,000 and 300,000 units respectively plus a total of 320 mg. of mapharsen given in eight divided doses of 40 mg. each daily for eight days. This mapharsen dosage was deliberately selected as a relatively safe and known subcurative dose from which a high rate of relapse might be expected.

Later, as material accumulated, the variable of time was brought under study, and three additional treatment groups were established with a total dosage of

The authors are members of the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council.

The work described in this paper was done under several contracts recommended by the Committee on Medical Research of the Office of Scientific Research and Development.

Read in a panel discussion on "Penicillin in the Treatment of Syphilis" before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

1. Mahoney, J. F.; Arnold, D. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**: 355, 1943.

2. Mahoney, J. F., and others: Unpublished data.

3. Eagle, H.: Unpublished data.

4. Dr. J. R. Heller Jr., medical director in charge Venereal Disease Division, United States Public Health Service, was later added to the membership of the panel.

5. The statistical data have been prepared by Miss Gwendolyn Futcher.

penicillin of 300,000, 600,000 and 1,200,000 units respectively given in thirty intramuscular injections every three hours day and night over a four day period. The latter groups have been so recently started as not to justify consideration in this paper, which is devoted entirely to the eight day treatment schedule. The only exception to the statement lies in 25 cases treated by the intravenous route before the present organized study began; in them the dosage was variable and the duration of treatment four to eight days.

TABLE 2.—*Duration of Follow-Up from Start of Treatment in 1,418 Patients with Early Syphilis (June 1, 1944)*

Duration of Follow-Up, Weeks	No. of Patients Followed
1 to 4	671
5 to 8	307
9 to 16	327
17 to 24	107
25 to 48	6

For the purposes of this report, the books of the Penicillin Panel have been temporarily closed as of May 25, 1944. To that date there had been received 1,587 case reports of early syphilis, of which 1,418 were suitable for analysis as to various points. Of these 177 had seronegative primary, 379 seropositive primary, 698 uncomplicated and 67 complicated [6] early secondary syphilis and 97 various types of recurrent (usually previously treated) secondary syphilis. Of the patients 461 were white, 950 Negro and 7 of other races; 791 were male and 627 female, of whom 58 were pregnant at the time of treatment.

The preliminary nature of this report is indicated by table 2, in which the duration of follow-up after treatment is shown. The majority of patients have so far been observed for less than two months; only 113 of the entire number for four months or longer. This fact must be repeatedly emphasized as a matter of caution; the results here presented are subject to major revision after further observation. It is planned to report further information as it develops at three to six month intervals.

THE IMMEDIATE RESULTS OF TREATMENT

Disappearance Time of Treponema Pallidum from Open Lesions.—Data are available on this point from 663 cases treated with penicillin alone (excluding those cases treated with penicillin plus mapharsen).

Regardless of the single or total dose of penicillin, organisms have promptly disappeared from open lesions in every case within a range of six to sixty hours. At the two extremes of dosage, 1,000 and 40,000 units, the average disappearance time varied only from twenty-one to fourteen hours. Whether the apparent trend toward shortening of disappearance time is significant is open to question because of the varying intervals at which dark field examinations were done in the several clinics. Not shown in the table is the fact that the intravenous holds no advantage over the intramuscular route in this respect.

Healing of Lesions.—This is difficult to measure in statistical terms. There has been no observed instance of failure of lesions to heal, regardless of the single or total dose. With a total dosage of 60,000 units in eight days, healing is less prompt than with arsenical therapy; with larger total dosage, 300,000 units and up, it is as rapid as with standard chemotherapy or more so.

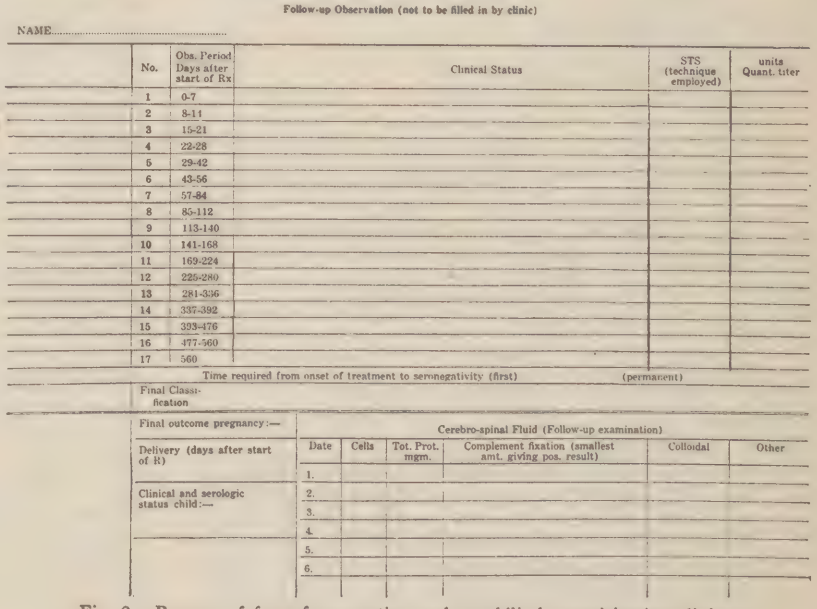
Serologic Response.—In figure 3 is shown the median blood serologic response,[7] in terms of quantitative titer, of four groups of patients treated with penicillin alone (excluding those treated with penicillin plus mapharsen). Included are both seropositive primary and secondary syphilis. Regardless of the total dosage, whether 60,000, 300,000, 600,000 or 1,200,000 units, there is apparent a trend toward serologic reversal within a period of about twenty days after the start of treatment. Within the range of 300,000 to 1,200,000 units this trend is approximately uniform, regardless of dosage; with 60,000 units it is a little slower and less pronounced. Parenthetically, this rate of serologic reversal is identical with that observed after arsenical chemotherapy, whether with an arsphenamine at weekly

TABLE 3.—*Average Disappearance Time of Treponema Pallidum from Open Lesions of Early Syphilis After Varying Treatment Schedules (June 1, 1944)*

Size of Individual Dose Given Every Three Hours, Units	Cases	Average Disappearance Time of Treponema Pallidum, Hours
1,000	52	21
5,000	201	20
10,000	237	19
20,000	135	13
40,000	38	14

6. Complicated by asymptomatic neurosyphilis, syphilitic meningitis or ocular, osseous or visceral lesions.

7. This has been determined by a statistical device which assigns to the initial quantitative titer, regardless of the actual number of units, the numerical value of 100. All subsequent observations are expressed in terms of per cent of the original titer.



Follow-up Observation (not to be filled in by clinic)

NAME.....

	No.	Obs. Period Days after start of Rx	Clinical Status	STS (technique employed)	units Quant. titer
	1	0-7			
	2	8-14			
	3	15-21			
	4	22-28			
	5	29-42			
	6	43-56			
	7	57-84			
	8	85-112			
	9	113-140			
	10	141-168			
	11	169-224			
	12	225-280			
	13	281-336			
	14	337-392			
	15	393-476			
	16	477-560			
	17	560			

Time required from onset of treatment to seronegativity (first) (permanent)

Final Classification

Final outcome pregnancy:—

Delivery (days after start of R)

Clinical and serologic status child:—

Cerebro-spinal Fluid (Follow-up examination)

Date	Cells	Tot. Prot. mgm.	Complement fixation (smallest amt. giving pos. result)	Colloidal	Other
1.					
2.					
3.					
4.					
5.					
6.					

Fig. 2.—Reverse of form for reporting early syphilis by participating clinics.

intervals or mapharsen given by various intensive methods.

Further data are shown in tables 4 and 5. In table 4 is summarized the blood serologic response of 48 patients with seronegative primary syphilis observed for nine or more weeks after the start of treatment. These are not broken down by total dosage since, regardless of the range of 60,000 to 1,200,000 units, the response was identical. In 28 patients the serologic test for syphilis, originally negative, remained so

TABLE 4.—*Blood Serologic Response in Seronegative Primary Syphilis, Patients Followed More Than Nine Weeks from Start of Treatment, All Treatment Schedules Combined (June 1, 1944)*

	Serologic Test for Syphilis		
Cases Followed	Negative, Remained Negative	Negative, Became Positive, Later Negative	Serologic Relapse
48	28	18	2

throughout the period of observation; in 18 it became temporarily positive, then reverted to negative, and in 2 only there was a subsequent serologic relapse. From the serologic standpoint, therefore, and during the very brief observation period so far available, the results may be said to be satisfactory in 95.8 per cent of the cases.

In seropositive early syphilis (combining seropositive primary and secondary syphilis) the results, now broken down by treatment schedule, are shown in table 5 (limited to patients observed for nine or more weeks after the start of treatment). Here there is a direct relationship between "satisfactory" and "unsatisfactory" immediate serologic results and total dosage of penicillin; the larger the dose, the better the result. The only and perhaps a major exception to this is in the group of patients who received 300,000 units of penicillin plus 320 mg. of mapharsen in seven and one-half days. This group shows as good initial results as were shown by patients receiving four times as much penicillin without mapharsen.

So far it is clear that the minimum effective dose of penicillin in early syphilis in man cannot be determined on the bases of disappearance time of surface organisms, healing of lesions or (except very roughly) serologic response since, regardless of total dose, within the range employed the drug is effective in all of these respects. The only available criterion lies, therefore, in the incidence of relapse.

TABLE 5.—*Blood Serologic Response in Seropositive Early Syphilis According to Treatment Schedule, Patients Followed More Than Nine Weeks from Start of Treatment (June 1, 1944)*

		Serologic Test for Syphilis Response	
Treatment Schedule, Units	Cases Followed	Satisfactory (Reversed, or Titer Falling), %	Unsatisfactory (No Significant Change, or Relapse), %
60,000	55	57.8	42.1
60,000 + mapharsen	26	76.9	23.0
300,000	79	82.1	17.7
300,000 + mapharsen	24	91.6	8.3
600,000	109	88.0	12.0
1,200,000	62	90.3	9.6

Relapse After Penicillin Treatment.—In this material, relapse has been rigidly defined. Any subsequent clinical manifestation of the disease, whether obviously relapse or apparently reinfection, has been classified as clinical relapse. Serologic relapse includes not only those who, originally seronegative or rendered so by treatment, subsequently became seropositive but also those who, still seropositive in low titer, subsequently develop high titer tests.[8] An effort has been made to

TABLE 6.—*Incidence of Relapse in Seronegative Primary Syphilis Treated by Varying Schedules in Eight Days, Patients Observed for More Than Thirty-Eight Days (June 1, 1944)*

		Relapse			
Treatment Schedule, Total Dose, Units	Cases Followed	Clinical	Serologic	Total Number	%
60,000	1	..	..	..	...
200,000	..	..	..	..	...
300,000	14	1	..	1	7.2
600,000	21	1	1	2	9.5
1,200,000	52	..	..	..	...
Intravenous (see text)	4	..	..	..	...
Total	92	2	1	3	3.2

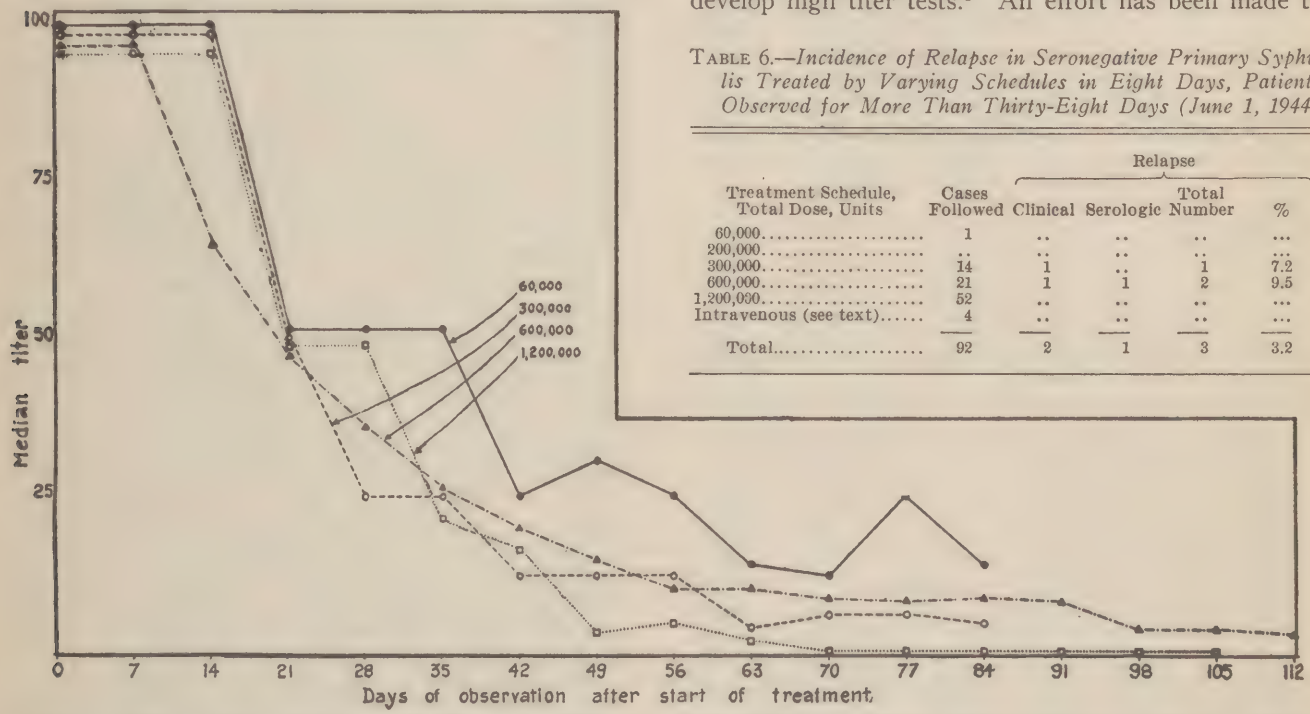


Fig. 3.—Median serologic response of seropositive early syphilis to penicillin with four treatment schedules ranging from 60,000 to 1,200,000 units total dose in eight days; June 1, 1944.

observe all patients clinically and serologically at weekly intervals for the first two months, every two weeks for another two to three months and at least monthly thereafter.

The number of relapses reported in this paper is minimal and less than the number which have actually occurred. This is due to (1) an inevitable lag in reporting from the individual clinic to the Penicillin Panel and (2) delay in defining apparent serologic relapse on the basis of a single observation until confirmed by subsequent tests (for the sake of avoiding laboratory error).

The method of statistical reporting here adopted is recognizedly inaccurate in that the incidence of relapse is related to the total number of patients observed for a period of time greater than that of the earliest observed relapse. In the tables to follow all patients are included who were observed for thirty-eight days or longer after the start of treatment, since this was the shortest interval at which relapse was observed. The brief interval available for study prevents the adoption of the statistical method used by Eagle,[9] which will, however, be utilized in later more definitive analyses. Preliminary rough test of this method of appraisal suggests that the eventual incidence of relapse will probably be from four to five times as great as that reported here. In table 6 is shown the incidence of relapse, clinical and serologic, in 92 patients with seronegative primary syphilis. The numbers, broken down by treatment schedule, are too small to be significant, though the total observed relapse rate, 3.2 per cent, is low.

Similar data for seropositive primary syphilis are shown in table 7 and for secondary syphilis in table 8.

TABLE 7.—*Incidence of Relapse in Seropositive Primary Syphilis, Treated by Varying Schedules in Eight Days, Patients Observed for More Than Thirty-Eight Days (June 1, 1944)*

Treatment Schedule, Total Dose, Units	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
60,000	8	2	..	2	25.0
200,000	3	..	..	..	....
300,000	30	2	1	3	10.0
600,000	37	..	..	..	....
1,200,000	75	1	1	2	2.6
Intravenous (see text)	5	1	..	1	20.0
Total	158	6	2	8	5.0

TABLE 8.—*Incidence of Relapse in Secondary Syphilis Treated by Varying Schedules in Eight Days, Patients Followed for More Than Thirty-Eight Days (June 1, 1944)*

Treatment Schedule, Total Dose, Units	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
60,000	37	9	2	11	29.6
200,000	8	3	..	2	37.5
300,000	94	6	4	10	10.6
600,000	136	4	3	7	5.0
1,200,000	64	..	2	2	3.1
Intravenous (see text)	16	1	1	2	12.5
Total	355	23	12	35	9.8

8. Not yet classified as relapse or "unsatisfactory result" are those patients whose serologic tests have shown no improvement. Twelve months after treatment will be allowed to elapse before such patients are classified as seroresistant.

9. Eagle, H.: The Treatment of Early and Latent Syphilis in Nine to Twelve Weeks with Triweekly Injections of Mapharsen: A Preliminary Analysis of the First 4.823 Cases, to be published.

These relate to patients treated with penicillin alone (excluding the combined penicillin with mapharsen groups). Here there is obvious a direct correlation between total dose and relapse incidence.

The data of tables 6, 7 and 8 are combined in table 9 for all patients with early syphilis; and here is added information concerning the patients treated with penicillin plus 320 mg. of mapharsen (two groups, 60,000 and 300,000 units respectively) and also concerning a small group of patients (25 in number) treated by the intravenous route before the present organized study was begun. In patients treated with penicillin by the intramuscular route the incidence of relapse, even in the brief observation period available, is in direct proportion to total dosage (nearly 30 per cent with 60,000 units, only 2 per cent with 1,200,000 units). In the small group who received large doses intravenously, ranging from 600,000 to 1,200,000 units, and whether by multiple injections or continuous drip, the observed relapses are five to six times as great as in patients treated with comparable doses by the intramuscular route, suggesting that the intravenous route not only holds no advantage over the intramuscular route but is actually less effective.

In table 10 the incidence of relapse is related to the stage of disease at the start of treatment in patients treated with penicillin alone (omitting the groups combined with mapharsen, among which only 1 relapse has so far occurred) and without regard to total dosage. In conformity with Eagle's report [9] as to semi-intensive arsenotherapy, and in contrast to the older Cooperative Clinical Group and other data [10] as to "standard" prolonged arsenical chemotherapy, there seems to be here a direct relationship between the stage of the disease at the time of starting treatment and the incidence of relapse. The proportions in patients treated with penicillin alone are 3.2 per cent for seronegative primary, 5.0 per cent for seropositive primary and nearly 10 per cent for early secondary syphilis.

Table 11 shows the average and extreme intervals between the start of treatment and observed relapse. Here there is no direct correlation as to total dose. Relapses have occurred as early as thirty-eight days and as late as two hundred and ninety-four days after the start of treatment Considering the short periods of observation so far available for all groups treated, further relapses in all may be confidently anticipated.

The Optimum Time-Dose Relationship for Penicillin in Early Syphilis.—The available data indicate that within the twentyfold dosage range employed in a period of seven and one-half days penicillin has a profound immediate effect in terms of disappearance of surface organisms, healing of lesions and serologic reversal. In seronegative primary syphilis no statements as to minimum effective dose are as yet justifiable. In seropositive primary and early secondary syphilis any dose less than 600,000 units in seven and one-half days is clearly ineffective. A total dose of 600,000 units provides a minimum relapse rate of nearly 5 per cent, of 1,200,000 units a rate of 2 per cent, within the short period for which such patients have so far been followed. The intravenous route appears to be less effective, even in large doses, than the intra-

10. Stokes, J. H., and others: Cooperative Clinical Studies in the Treatment of Syphilis: Early Syphilis, Ven. Dis. Inform. **13**: 165, 207 and 253, 1932.

muscular.

The possibility that even 1,200,000 units in a four to eight day period will prove to be inefficacious after further observation has led the Penicillin Panel to inaugurate the study of two additional treatment groups

TABLE 9.—*Incidence of Relapse in All Types of Early Syphilis Treated by Varying Schedules, Patients Observed for More Than Thirty-Eight Days (June 1, 1944)*

Treatment Schedule, Total Dose, Units (Route Intramuscular Unless Specified)	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
60,000	46	11	2	13	28.2
60,000 + 320 mg. mapharsen	26	..	..	..	....
200,000	11	3	..	3	27.2
300,000	138	9	5	14	10.1
300,000 + 320 mg. mapharsen	68	1	..	1	1.4
600,000	194	5	4	9	4.6
1,200,000	191	1	3	4	2.0
Various intravenous schedules *	25	2	1	3	12.0

* Dosage range 600,000 to 1,200,000 (all but 3 cases 1 million +), single intravenous injections, intravenous drip or both, in 4 to 8 days.

TABLE 10.—*Incidence of Relapse by Stage of Disease, All Treatment Schedules* Combined, Patients Followed More Than Thirty-Eight Days (June 1, 1944)*

Stage of Disease	Cases Followed	Relapse			
		Clinical	Serologic	Total Number	%
Primary seronegative	92	2	1	3	3.2
Primary, seropositive	158	6	2	8	5.0
Secondary	355	23	12	35	9.8

* Omitting 94 patients treated with penicillin + mapharsen.

given a total of 2,400,000 units in thirty and sixty intramuscular injections in four and seven and one-half days respectively. These patients are being treated in the United States Army and eight selected United States Public Health Service rapid treatment centers.

The results obtained to date in the two small groups of patients given 60,000 and 300,000 units of penicillin respectively, in each case plus the known subcurative total dose of 320 mg. of mapharsen in eight days, are worth emphasizing. In 94 such patients followed for thirty-eight days or more only one relapse has occurred. It is perhaps to be expected that certain patients with early syphilis will prove to be resistant to penicillin exactly as a relatively standard proportion of 5 to 15 per cent of patients has proved to be resistant to arsenic heavy metal chemotherapy. But, in view of what is already known concerning the probable modes of action of penicillin and of arsenic and bismuth in syphilis (considerations too lengthy for discussion here) it is possible that those patients resistant to penicillin will not be the same ones resistant to metal chemotherapy and that a combination of the two forms of treatment will eventually prove to be more effective than any method of use of either one alone.

It should also be emphasized that penicillin, as so far employed in early syphilis, is not suitable for mass application. Injections every three hours day and night over whatever period of time demand hospitalization and trained nursing or professional care. However available these may be for the armed forces, facilities are inadequate in civilian practice to meet the enormous demand. The eventual general use of the drug depends

TABLE 11.—*Average and Extreme Intervals from Start of Treatment to Relapse According to Treatment Schedule (June 1, 1944)*

Treatment Schedule, Units	Average Interval, Days	Extreme Intervals, Days
60,000	104	64 to 154
60,000 + mapharsen	No relapses observed	
200,000	116	83 to 135
300,000	90	38 to 166
300,000 + mapharsen	..	53*
600,000	98	73 to 113
1,200,000	132	63 to 294
Intravenous	74	56 to 126

* One relapse only.

on the development of methods which will permit its administration on an ambulatory basis.

As with arsenical chemotherapy, it is probable that the optimum time-dose relationship for the treatment of early syphilis in man with penicillin alone and its relative efficacy when administered alone or in combination with other forms of treatment will be guided by data from the experimental laboratory not as yet available but shortly to be expected.

In man, further immediate studies should be directed to (1) determination of the relative effectiveness of 1,200,000 units versus much larger doses in four and eight days respectively, (2) variation of the time interval between individual dosage within the range of three to twenty-four hours, (3) more exact definition of the merits of intravenous versus intramuscular administration and (4) an expansion of the combinations penicillin plus arsenic and penicillin plus bismuth.

Results of Treatment of Special Forms of Early Syphilis.—Thirteen patients with early syphilis in this series had positive spinal fluids before treatment (11 of them group 2, 2 group 3). Of these, the fluid abnormalities disappeared or improved under penicillin treatment alone in 10 within time period ranging from ten to fifty days; 3 were unimproved.

Acute Syphilitic Meningitis.—Ten patients with this complication of early syphilis have been treated, the majority with 1,200,000 units in seven and one-half days. Symptomatic relief has been dramatically prompt in all and, in the majority, spinal fluid abnormalities have disappeared or are rapidly improving.

Treatment Resistant Early Syphilis.—Eight patients, most of them with dark field positive psoriasiform syphilids, persisting in spite of or recurring during metal chemotherapy, have been treated with penicillin, with prompt healing in all and with subsequent serologic behavior similar to that of previously untreated early syphilis.

Infantile Congenital Syphilis.—Not included in the tabular presentations are some 20 infants with early congenital syphilis. The majority of them have been treated with a total dose of penicillin of 20,000 units per kilogram of body weight, corresponding to a total dose of 1,200,000 units in the adult. Their behavior in terms of symptomatic improvement and serologic response is analogous to that of early acquired syphilis in the adult.

The Outcome of Pregnancy.—Though 58 pregnant women with early syphilis have so far been treated, it is too early to speak of any results as to the outcome in the child.

Herxheimer Reactions.—Of 1,418 patients treated, 846 (59 per cent) have had Herxheimer reactions within the first twenty-four hours. This consists usually of fever alone (685 cases); in the others, exacerbation of secondary skin lesions with or without fever. The fever is usually mild (less than 102 F.), though in 174 cases (12 per cent) the febrile rise has been higher than this level. In no case has the reaction been alarming, nor has it interfered with subsequent treatment.

Other Reactions.—Only 59 patients (41 per cent of the total treated) have had other reactions attributable to penicillin. In 15 there were cutaneous eruptions (8 urticaria, 7 other types of skin rashes, none severe). Seven had mild gastrointestinal reactions, 33 secondary fever, 2 abscessed buttocks and 2 miscellaneous mild disturbances. In no case has penicillin treatment had to be suspended because of reactions from the drug.

SUMMARY

1. An organized study of the effect of penicillin in early syphilis is in progress in an effort to determine the optimum method of use of the drug. The results so far available are preliminary.

2. Penicillin has a profound immediate effect in early syphilis in terms of (*a*) disappearance of surface organisms from open lesions, (*b*) healing of lesions and (*c*) a trend toward serologic reversal.

3. These immediate effects are in general identical within a twentyfold dosage range of 60,000 to 1,200,000 units administered by the intramuscular route every three hours day and night to a total of sixty injections in seven and one-half days.

4. The same immediate effects are apparent within the dosage range of 300,000 to 1,200,000 units given by the intramuscular route every three hours day and night to a total of thirty injections in four days.

5. These immediate effects cannot be utilized to determine the optimum time-dose relationship, which, in man, depends on the incidence of relapse.

6. The incidence of relapse, when penicillin is administered alone, is in direct relationship to the total dosage given by the intramuscular route in a seven and one-half day period, greatest with 60,000 units and least with 1,200,000 units.

7 Relapse appears to be more frequent after intravenous than after intramuscular administration of comparable doses.

8. The lowest incidence of relapse—and the most favorable serologic response—was in small groups of patients treated with 60,000 and 300,000 units respectively of penicillin plus a known subcurative dose of mapharsen.

9. Penicillin has a favorable effect in early asymptomatic neurosyphilis, acute syphilitic meningitis, early syphilis treatment resistant to arsenic and bismuth and infantile congenital syphilis.

10. No opinion can be as yet expressed as to the effect of penicillin in the prevention of prenatal syphilis.

11. The optimum time-dose relationship of penicillin in early syphilis is not yet established. Certainly the minimum dose, especially in secondary syphilis, should not be less than 1,200,000 units; probably it should be more.

12. Herxheimer reactions after the penicillin treatment of early syphilis are frequent but not serious; other reactions, due to penicillin itself, are negligible.

13. Further avenues of study are suggested.

THE ACTION OF PENICILLIN IN LATE SYPHILIS

INCLUDING NEUROSYPHILIS, BENIGN LATE SYPHILIS AND LATE CONGENITAL SYPHILIS: PRELIMINARY REPORT

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These cases are drawn from eight clinics at present engaged in a study of the effect of penicillin on late syphilis, under the general auspices of the Committee on Medical Research of the office of Scientific Research and Development. These, with the names of the responsible investigators, are as follows: University of Pennsylvania (John H. Stokes, M.D.), Cornell University (Walsh McDermott, M.D.), Mayo Clinic (Paul A. O'Leary, M.D.), Boston Psychopathic Hospital (Harry P. Solomon, M.D.), University of Michigan (Udo J. Wile, M.D.), Bellevue Hospital (Evan Thomas, M.D.) and Johns Hopkins University (J. E. Moore, M.D.). Associated with each of them are various co-workers and assistants too numerous to mention here, but to whom due credit will subsequently be given.

Penicillin has distinctly beneficial serologic and clinical effects on neurosyphilis, including early and late manifestations, not excepting tabes and paresis, and including asymptomatic neurosyphilis. Its action on gummatous manifestations of skin, mucosae and bones is so striking and complete that it seems unnecessary to collect further cases merely to demonstrate it as such. In ocular syphilis, simple inflammatory processes respond; later and more complicated lesions such as the optic neuritides and interstitial keratitis recover, relapse, present resistance and residues proportional to damage already done. This statement is probably true of visceral syphilis and of special localized processes and eighth nerve involvement.

These categorical statements are based on a material collected from 182 cases, observed for periods ranging

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The authors are members of the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council.

The work described in this paper was done under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and several universities.

Read in a panel discussion on "Penicillin in the Treatment of Syphilis" before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

from eight to two hundred and fourteen days after the institution of treatment. The preliminary conclusions are sharply limited by qualifications involving not only duration of observation and small numbers in individual breakdown items but by wide variation in time-dosage relationships and little uniformity as to time and type of test and recheck procedure. No precedents existing, each investigator groped his way into his problem. A considerable part of the material collected from nonuniform records was of such short observation and so "mixed" in therapeutic procedure that it furnished little evaluative worth. The distribution by source, duration of observation and diagnosis is given in table 1. Paresis, a crucial tester of therapeutic effect, heads the list (56 cases) and neurosyphilis totals 122 cases. Observation of sixty days or more was maintained in 44 Pennsylvania, 20 Johns Hopkins, 11 Mayo, 1 Bellevue, 5 New York Hospital and 1 Michigan case, a total of 82 cases.

Notwithstanding the limitations described, the material furnished the basis for demonstrating by both symptoms and laboratory tests (quantitative serologic, spinal fluid examination) the incontestable reality of the effect of penicillin treatment in syphilis. It permits an exploratory breakdown into grades of treatment effect as such, in relation to previous standard treatment; by at least two grades of intensity of penicillin treatment—low intensity (type A) 600,000 to 1,200,000 units of the sodium salt at 10,000 to 25,000 units intramuscularly every three to four hours and high intensity (type B) 2,400,000 to 4,000,000 units at 25,000 to 50,000 units intramuscularly every two to four hours. It was not possible from this material to estimate the difference in effect of hourly variations or unit dose variations, or of intravenous or intraspinal medication.

EFFECT OF PENICILLIN ON THE REAGIN TITER OF THE BLOOD

Irrespective of the system used and in all types of late (excluding latent) syphilis, penicillin causes improvement (reduction) of reagin titer in from about 50 to 60 per cent of 96 late cases in which such data were available (table 2) An initial Herxheimer-like rise or "provocative" effect is observable in about 20 per cent of late cases. Within the period of observation 10 per cent of late cases became completely negative.

In 5 cases of seroresistant syphilis, 1 became negative (low titer to start with) and 4 improved. Herxheimer effect occurred in 1.

In 32 cases of general paresis, disregarding treatment system employed, 16 were serologically improved, 2 reduced to negative.

EFFECT OF PENICILLIN ON THE SPINAL FLUID IN NEUROSYPHILIS

This furnishes probably the most graphic demonstration of the effect of penicillin, because of its multiple quantitative approach. Seven grades of change were considered: worse, no change and five grades of improvement as follows: grade 1, reduction in cell count or total protein; grade 2, reduction in both cell count and total protein; grade 3, reduction of cell count, total protein and intensity of colloidal test; grade 4, reduction in cells and protein and in intensity of both colloidal and complement fixation tests; grade 5, return to normal.

In grouping improvements, grades 1 and 2 together were rated as slight, grades 3, 4 and 5 together as definite improvement. Improvement as a whole, however, included grades 2, 3, 4 and 5.

TABLE 1.—*Penicillin Investigation: Late and Miscellaneous Syphilis; Distribution of Material by Source, Duration of Observation and Diagnosis*

Diagnosis	Duration of Observation: Immediate: Less Than 20 Days	20-59 Days	60-99 Days	100-139 Days	140-214 Days	Total Cases
Paresis and taboparesis	11	22	15	4	4	56
Tabes, including primary optic atrophy	6	8	5	2	1	22
Meningovascular neurosyphilis	6	3	3	3	1	16
Asymptomatic neurosyphilis	2	13	8	1	4	28
Benign late skin and bone	4	8	3	0	6	21
Interstitial keratitis	0	5	3	3	2	13
Iritis	0	2	1	0	1	4
Miscellaneous	4	6	5	6	1	22
Total						182
Clinic sources						
Bellevue	1	3	1	0	0	5
Boston	8	8	0	0	0	16
Johns Hopkins	9	23	10	2	8	52
Mayo	7	3	6	1	4	21
Michigan	6	2	1	0	0	9
New York Hospital	1	10	5	0	0	16
Pennsylvania	1	18	20	16	8	63
Totals	33	67	43	19	20	182

TABLE 2.—*Blood Serologic Response to Penicillin*

Type of Syphilis	Herxheimer or Provocative Effect	Improved But Not to Negative	Reduced to Negative	Improvement Temporary	No Change
Late (96 cases)	20	33	10	13	25

TABLE 3.—*Cerebrospinal Fluid Changes Following Penicillin in 107 Cases in Which Repeated Spinal Fluid Examinations Were Available at Some Time After Treatment*

Diagnosis	Slight Improvement: Grade 1 Cells or Protein Reduced	Slight Improvement: Grade 2 Cells and Protein Reduced	Definite Improvement: Grade 3 Cells Protein Colloid Reduced	Definite Improvement: Grade 4 Cells Protein Colloid and Wassermann Reduced	Definite Improvement: Grade 5 Return to Normal	No Change	Worse
Paresis and taboparesis (42 cases)	6	19	4	4	0	5	4
Tabes and meningovascular (25 cases)	4	2	4	7	0	5	3
Asymptomatic (40 cases)	7	5	6	9	1	6	6
Total (107 cases)	17	26	14	20	1	16	13

In a total of 107 cases which had had one or more spinal fluid examinations after completion of penicillin therapy, it appears that 78 cases showed some degree of improvement in spinal fluid findings, 43 slight and

35 definite. The commonest change is a reduction in cells and total protein, but grade 4 improvement is remarkably common, including all four items of the fluid examination. This response is, as would be expected, evident in a higher proportion (1/4) in asymptomatic neurosyphilis than in paresis (1/9). Some of the cases rated as "worse" are, we believe, to be regarded as Herxheimer or flare effects and would probably improve on longer observation. It is interesting that 4 asymptomatic cases accompanied by gummatous benign syphilis were among the 6 asymptomatic cases in which the condition became "worse."

In order to carry the specific touch of conviction to the doubter as to the effect of penicillin on the blood and spinal fluid, we reproduce here serial spinal fluid and blood observations of 6 patients, 3 with late con-

TABLE 4.—*Penicillin Treatment Series 1 in Case 3; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	16 units	29	0123	3 plus	4432210000
13	.....	12	0012	2 plus	2211000000
76	2	10	0112	1 plus	3211000000

TABLE 5.—*Penicillin Treatment Series 2 in Case 3; Total Additional Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
104	16 units	11	0112	20 mg.	2211100000
164	Less than 1	5	0012	20 mg.	2211000000

TABLE 6.—*Penicillin Treatment Series 1 in Case 5; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	128 units	22	1244	4 plus	1333320000
19	16	8	1244	3 plus	4431100000
55	32	4	0012	Plus-minus	2221000000
86	64	3	0123	30	2221100000
111	64	1	0124	50	2211000000

genital syphilis and 3 with acquired neurosyphilis. It is notable that these effects were secured with low intensity (type A) treatment in all but 1 case.

CASE HISTORIES

CASE 3 (Pennsylvania).—A man aged 38, with acquired syphilis. Primary optic atrophy in tabes, with euphoria, possible taboparesis. Fields (fig. 2) showed sector defect suggesting arachnoiditic or retrobulbar neuritic episode. Original spinal fluid, cells 122, Kolmer Wassermann reaction 4444, Pandy 4 plus, mastic 4442110000, improved to cells 29, Kolmer Wassermann reaction 0123, Pandy 3 plus, mastic 4432210000 by two Swift-Ellis treatments. After the first series of treatments with penicillin (table 4) the patient began to lose ground visually, with slight confusion and increased euphoria. The second series of treatments (table 5) resulted in definite improvement in fields, acuity and mental state.

CASE 5 (Pennsylvania).—A man aged 24 with congenital syphilis with typical stigmas, asymptomatic neurosyphilis, previously treated with forty arsenical and forty bismuth injections, was given the treatment outlined in table 6. He was retreated twenty-eight days later with the results shown in table 7.

CASE 11 (Pennsylvania).—A man aged 18 with congenital syphilis discovered at age 6 and treated with thirty neoarsphenamine injections a year for eleven years showed typical stigmas, neurologic signs, including Argyll Robertson pupils, anisocoria, partial ptosis of the left eyelid, weakness of the left seventh nerve and sluggish reflexes. He was given the treatment outlined in table 8. The ptosis disappeared under penicillin.

CASE 8 (Pennsylvania).—A woman aged 41 with acquired asymptomatic neurosyphilis discovered in blood donation, without symptoms or previous treatment, was given penicillin with the results shown in table 9.

CASE 29 (Pennsylvania).—A woman aged 29 with acquired neurosyphilis experienced sudden diminution of vision, advanced primary optic atrophy. Previous treatment, 1935-1939, consisted of eighteen arsphenamine and thirty-six bismuth injections. Treatment with penicillin (table 10) resulted in no improvement in fields or acuity: right eye 20/400, left eye 20/300.

CASE 50 (Pennsylvania).—A man aged 25 with congenital syphilis, showing typical stigmas and asymptomatic neurosyphilis, had been treated with sixty-two injections of neo-

TABLE 7.—*Penicillin Retreatment Series 2 in Case 5; Total Additional Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
139	64 units	2	0011	40	2211000000
164	64	4	0011	20	1110000000

TABLE 8.—*Penicillin Treatment Series 1 in Case 11; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	16 units	32	1244	4 plus	3332210000
13	4	16	0122	1 plus	2111000000
32	4	8	0011	Plus-minus	1111000000
140	Less than 1	1	0000	30 mg.	1110000000

arsphenamine and 102 injections of bismuth. Results of treatment with penicillin are shown in tables 11 and 12.

CASE 64 (Pennsylvania).—A man aged 37 with acquired syphilis, early paresis (?), showed sluggish pupils and lower cord reflexes and loss of memory. Previous treatment consisted of twenty-two mapharsen injections and nineteen bismuth injections.

SYMPTOMATIC RESULTS IN NEUROSYPHILIS

Since there is a well recognized disparity between symptomatic and serologic response in neurosyphilis, and the symptomatic often outweighs the serologic aspect in importance for the patient, symptomatic responses secured by penicillin in neurosyphilis were next examined. Here it is important to give warning of misinterpretations due to Herxheimer and possibly therapeutic paradoxical effects from overintense initial treatment. It is notable that some patients who did badly at the start improved later and that top notch symptomatic gains followed a low intensity system in some cases.

Penicillin also has a favorable effect in general paresis. Three groups were made up from the material (conceding the inadequacy from the psychiatric standpoint due to record deficiencies): simple demented paresis (grades 1, 2 3); deteriorated paresis (grades 1, 2, 3); progressive paresis (galloping and so on) and symptomatic exacerbation suggesting Herxheimer effect. Improvement was graded 25, 50 and 75 and 100 per cent, the last representing practically complete restoration to normality.

Of 56 cases of paresis and taboparesis, 10 presented no adequate classification data. Of the 46 remaining cases 30 were classified as simple demented, of which

TABLE 9.—*Penicillin Treatment Series 1 in Case 8; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	64 units	103	4444	4 plus	2444411000
17	8	29	1244	2 plus	2221100000
46	32	11	0012	1 plus	2211000000
74	32	6	0112	30	1111000000
102	32	6	0112	40	2211000000
129	8	4	0011	30	1111000000
159	32	8	0122	30	2211100000
178	16	6	0012	30	2221100000

TABLE 10.—*Penicillin Treatment Series 1 in Case 29; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	64 units	148	4444	30 mg.	3331100000
9	64	16	1244	30 mg.	2221100000
30	32	15	0012	30 mg.	2221000000
65	64	4	0122	20 mg.	1111000000
119	32	0	0011	20 mg.	1111000000

TABLE 11.—*Penicillin Treatment Series 1 in Case 50; Total Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	16 units	96	4444	40 mg.	2455555421
8	Negative	21	4443	20 mg.	4443210000
36	32	12	0124	30 mg.	2221000000

TABLE 12.—*Penicillin Retreatment Series 2 in Case 50; Additional Dose 1,200,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
53	Negative	5	0112	30 mg.	2221100000
84	16 units	3	0000	20 mg.	1111000000

TABLE 13.—*Penicillin Treatment Series 1 in Case 64; Total Dose 2,850,000 Units*

After Penicillin, Days	Quantitative Kline (Blood)	Cerebrospinal Fluid			
		Cells	C. S. F. Wassermann (Kolmer)	Protein	Mastic
0	Less than 1 unit	72	4444	40 mg.	3555521000
22	00	5	0011	20 mg.	1111000000
56	00	5	0012	20 mg.	1111000000

only 6 (20 per cent) failed to improve and 1 grew worse. Thirteen, or nearly half, improved 50 per cent or more, including 8 which improved 75 per cent and 1 restored symptomatically to normal. Ten cases improved only 25 per cent. As might be expected, deteriorated cases (10) made less response, 1 improving 50 per cent, 2 75 per cent and 7 showing no change. The 1 patient with progressive or galloping paresis in Solomon's service died and 1 of Moore's simple demented patients died thirteen weeks after penicillin.

We know of no record of spontaneous remission under the good effects of hospitalization which can

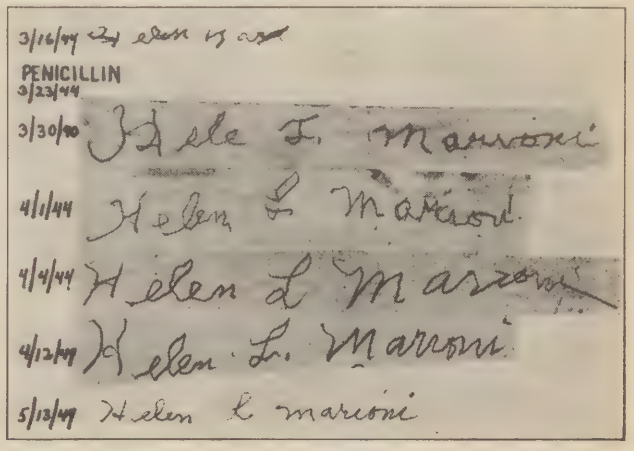

Fig. 1.—Improvement in handwriting of a simple demented paretic patient approximately six weeks after penicillin treatment. The signature before treatment is given above the word "penicillin" (courtesy of George D. Gammon, M.D.).

approach this. The transformations in orientation, speech, handwriting and encephalographic findings will be more fully presented from the University of Pennsylvania material in objective form by George D. Gammon, M.D., in a forthcoming paper. From the collected records, however, two brief summaries are given:

A white woman aged 34 with symptomatic paresis, grade 4 cerebrospinal fluid, could not write or do housework. She had auditory hallucinations, personality changes, disorientation, tremor of the tongue, hands and mouth, and slurred speech. On the second day of penicillin therapy she had a Herxheimer reaction with right-sided convulsions becoming generalized. After twenty-four hours penicillin was reinstituted at half dose to a total of 1,200,000 units without untoward effect. By the sixteenth day the patient was completely oriented, with memory, speech, tremor and electroencephalogram improved. In four months the patient was tremor free, speech and writing were normal (fig. 1), she was well oriented and hallucination free and was satisfactorily performing housework including marketing with points and driving a car. Clinical improvement was not accompanied by improvement in the spinal fluid.

A white man aged 42 with symptomatic paresis developed

mispronouncing of words, garbled speech, uncertain gait, tremor of hands and difficulty in writing in August 1943, when a shell exploded near him. Forty-eight arm and hip injections were given. He became boastful, speech rambled and tremors were more pronounced; handwriting was worse and calculation poor. His condition was unimproved during hospitalization after 50,000 Oxford units per dose of penicillin to a total of 4,000,000 units. Clinical improvement occurred three weeks after penicillin with loss of tremors, improved handwriting and speech. He passed an examination as a pipe fitter. Improvement in the cerebrospinal fluid did not accompany clinical improvement. The neurologist considered him mentally improved but not to the original level.

Combining all types of clinically diagnosed paresis and taboparesis, exclusive of 10 patients treated with intraspinal or intravenous penicillin or malaria and thus totaling 46 cases, 15 failed to improve, 12 improved 25 per cent, 6 improved 50 per cent, 10 improved 75 per cent, 1 recovered and 2 died. Of 22 patients with tabes dorsalis, 14 presented data sufficient for interpretation, including 7 with primary optic atrophy and 3 with lightning pains of unusual severity plus 4 taboparetic patients with lightning pains who were grouped together with respect to this symptom. Of the 14 tabetic patients 3 improved to the extent of 50 per cent or more, and 2 of them with lightning pains were relieved completely. Eleven tabetic patients showed no change. Of the patients with primary optic atrophy none were made worse, and 1 whose visual fields are shown (fig. 2) improved slightly but definitely in both fields and visual acuity, with concomitant improvement in the spinal fluid. There is some question as to whether the sector defect in the left field is not a residue of a retrobulbar neuritic process. Of the total of 7 patients with lightning pains, 2 were completely relieved, 1 improved 50 per cent, 2 improved 25 per cent, 1 was unchanged and 1 became worse.

Of 16 patients with various forms of meningovascular neurosyphilis, 6 presented no data on clinical improvement. Of the remaining 10, clinical improvements of 75 per cent were observed in 2, 50 per cent in 2 and 25 per cent in 2, with 3 showing no change and 1 becoming worse.

It is of course difficult to evaluate symptomatology into which elements of the subjective and the influence of suggestion, rest, practice (as in eye and station and gait tests) enter. The intervention of trifling or routine medication (as in the eye, for example) with improvement found to have begun before penicillin, and hence perhaps merely spontaneous or progressive, must be interpreted by long periods of observation. Symptomatology which is highly complex and of uncertain origin, such as lightning pains, in which the influence of the penicillin on other infective backgrounds may play a part, must be interpreted at this stage with reserve. There seems, however, to be a favorable trend in the evidence pointing to genuine and indeed rapid good effect on the disease process, supported by such objective detail as handwriting change, encephalograms, disappearance of ptosis and of violent headache associated with meningitis. Coupled with the objective changes in the spinal fluid, such evidence would seem to deserve great weight. It is, however, unreasonable to expect penicillin to restore degenerations and replace neurons.

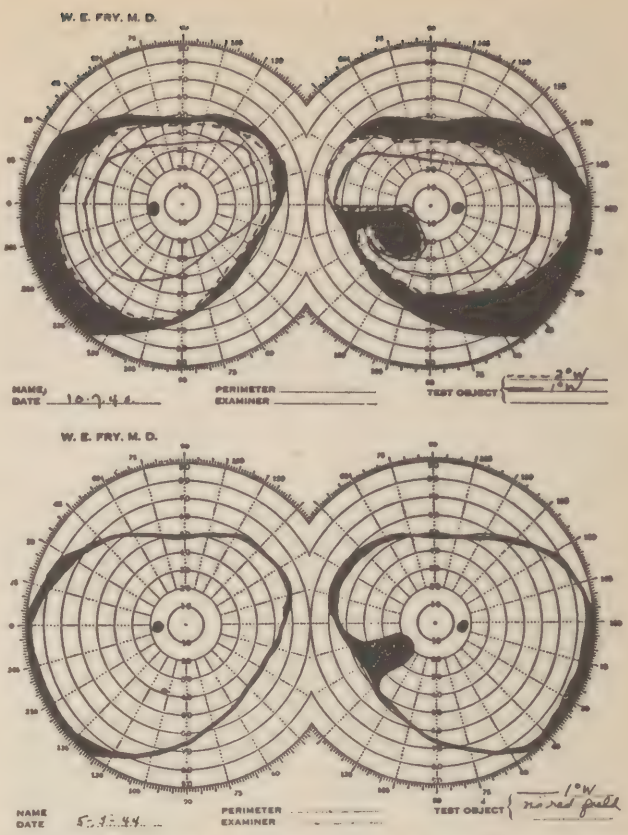

Fig. 2.—Visual fields in case 3, Pennsylvania Penicillin Series, showing improvement with decrease in sector defect.

EFFECT OF TREATMENT SYSTEM

In this material the lack of system in dosage and time intervals reduced the number of cases per recognizable system below statistically usable levels, especially when viewed in relation to duration of observation. Some cases were jumbles of methods and had to be discarded. There were no blood level determinations, and in 3 Mayo Clinic cases spinal fluid penicillin determinations were repeatedly negative. Accordingly, only a study of type A versus type B treatment was attempted, type A representing 1,200,000 units or less, usually at 25,000 units every three to four hours, and type B 2,400,000 units to 4,000,000 units or more at 25,000 to 50,000 every two to four hours. Offhand there was no striking difference recognizable between the effect of shorter time intervals or larger doses except the induction of Herxheimer reactions, which could be avoided by reduction in the dosage of the first twenty-four to forty-eight hours. The analysis of the case material on which treatment information was sufficiently complete for classification, comprising 105 cases, is given in tables 14 and 15.

It must be clearly recognized that such figures as these do not provide for trustworthy therapeutic inter-

TABLE 15.—*Degree of Cerebrospinal Fluid Improvement*

Type of Treatment	Number of Cases	Slight, Grade 1, 2	Moderate to Definite, Grades 3, 4, 5	No Change or Worse
Type A	36	8 (22.2%)	16 (44.4%)	12 (33.3%)
Type B	68	35 (51.4%)	19 (27.9%)	14 (20.5%)

pretations. It is particularly in point that the observation periods on the type B (larger dose) treated cases are shorter than those of type A and that a longer observation period may demonstrate a greater efficiency of larger dosage. On the other hand, it is also suggested that in late neurosyphilis good effects may be secured by less than the maximum dosage so far employed. If patients treated with 1,200,000 units in asymptomatic neurosyphilis can achieve almost normal spinal fluids and completely achieve them on retreatment with a similar dosage, a steplike method of successive moderate applications of treatment as distinguished from a single massive session would seem to deserve further study. Pushing the patient over the hump, so to speak, to a partial self cure is a recognized principle in dealing with some aspects of late neurosyphilis.

Serologic response on the blood occurred in 45 per cent of the type A or smaller dose treatment cases, and in 43 per cent of the larger dose or type B cases. Longer observation periods for the type B cases would probably demonstrate a superior effect.

PENICILLIN RESPONSE IN RELATION TO INFLAMMATORY ACTIVITY

Using the cell count and the spinal fluid as a guide and rating 0 to 20 as low, 21 to 60 as medium and 61 and above as high cell counts, an attempt was made to see whether improvement was greater in cases showing a high cell count as an index of definite inflammatory activity in comparison to those showing low cell counts. With cell counts rated as high, improvement occurred in 11 of 31 cases; with those rated as medium, in 13 of 28 cases; in those rated as low, in 7 of 45 cases. It appears that the proportion of improvement is highest in patients with medium and high cell counts in the order named and lowest in patients with low cell counts. If all cell counts above 20 are rated as high, improvement occurs in 24 of 59 cases in the higher cell count brackets (40.6 per cent) and in 7 of 45 in the low cell count bracket (15.5 per cent). Considering the small numbers of cases and the arbitrary division lines, the figures cannot be more than suggestive that, as has been previously indicated, a low cell count has a less favorable prognosis under penicillin treatment than a high cell count.

INFLUENCE OF PREVIOUS (ARSENIC, HEAVY METAL) TREATMENT ON PENICILLIN RESPONSE

An analysis of 100 cases of neurosyphilis with data on this matter yielded the results shown in table 16. The results in this case included grade 1 as well as grades 2, 3, 4 and 5. The type of previous treatment approximated the captions given, the first numeral representing arsenical, the second heavy metal injections.

Almost equally good results in the spinal fluid were achieved by penicillin after no previous treatment and intensive (40-80) routine treatment. There is at least no intimation that previous fever therapy prepared the patients for striking penicillin results. The many qualifications on such an analysis with regard to selection, time of observation and so on must be recalled, but there is at least no strong evidence that in the aggregate previous standard treatment adds anything to the penicillin result.

PENICILLIN IN OTHER ASPECTS OF LATE SYPHILIS

Gummatous lesions of skin and bones (21 cases) respond so invariably and completely, with 13 results rated 100 per cent, 2 at 75 per cent, 4 questionable and only 2 failing of improvement (thirty-six and sixty-eight days), that little further clinical interest attaches to the group beyond speculation as to the part played by penicillin in clearing the secondary, usually hemolytic pyogenic infective invasion as distinguished from the syphilis as such. The control of destructive lesions of the palate and septum seems satisfactory. The failures include one suspected gumma of the orbit, diagnosis not established. The dosage required for symptomatic improvement ranges about 300,000 units, the time for healing from twelve to forty-six days. Carcinoma as a complication or a diagnosis must be watched for

TABLE 16.—*Spinal Fluid and Clinical Improvement in Neurosyphilis After Penicillin Treatment in Relation to Previous Treatment*

Type of Previous Treatment	Clinical Improvement Grade 1 and Over Occurred in:	Spinal Fluid Grades 1, 2, 3, 4, 5 Occurred in:
No treatment	16 of 32, or 50 per cent	28 of 32, or 87 per cent
Little treatment	9 of 23, or 39 per cent	16 of 23, or 69 per cent
20 arsenic, 20 heavy metal	7 of 16, or 48 per cent	9 of 16, or 56 per cent
40 arsenic, 80 heavy metal	5 of 16, or 30 per cent	13 of 16, or 81 per cent
Fever therapy	1 of 13, or 7 per cent	5 of 13, or 46 per cent

TABLE 14.—*Effect on Spinal Fluid of Type A (Small Dose) Versus Type B (Larger Dose) Treatment*

	Grade of Response													
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		No Change		Worse	
Type of Neurosyphilis	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Paresis and taboparesis	1	5	2	15	1	2	3	1	0	0	1	3	1	2
Tabes	1	3	0	1	0	1	2	2	0	0	0	5	1	0
Meningovascular	0	2	1	1	1	3	3	0	0	0	0	0	0	1
Asymptomatic	1	6	2	3	1	5	4	5	1	0	3	3	6	0
Grade totals	3	16	5	20	3	11	12	8	1	0	4	11	8*	3
Total type A	36		56		36		36		36		36		36	
Total type B		69		69		69		69		69		69		69

* Four of these patients had benign gummas healing under penicillin at a wholly inadequate dosage for neurosyphilis—less than 600,000 units.

Grade 1 and 2 (slight) improvements occurred in 22 per cent of type A and 52 per cent of type B cases.

Grades 3, 4 and 5 (definite) improvement occurred in 16 of 36 cases (44 per cent) on type A treatment and 19 of 69 cases (27.4 per cent) on type B treatment.

Grades 2, 3, 4 and 5 improvement occurred in 60 per cent of the type A and 56 per cent of the type B cases. The periods of observation, however, were longer in the smaller dose treatment cases—e. g., paresis, over sixty days in type A; less than sixty days in all but 5 in type B cases.

even if improvement occurs. Concomitant neurosyphilis was identified in 12 of the 21 cases. Serologic improvement (titer reduction) in the blood occurred in 14 of 21 cases.

The paradox of gummatous skin and bone lesions healing as the spinal fluid became "worse" (possible Herxheimer effect?) was noted in 3 of 10 cases.

LATE CONGENITAL SYPHILIS

The interest in this group centers on interstitial keratitis. The neurosyphilitic involvements were reviewed with neurosyphilis (see cases 5, 11 and 50). The complexity of interstitial keratitis and the eccentricities of its behavior are apparent under penicillin as under standard treatment. It was difficult to dissuade those in charge of some patients to withhold fever and other treatment if the patient did not immediately and strikingly improve. Patients with pronounced corneal and other ocular damage were included and too much was expected in the way of results. Of 14 cases 6 showed improvement, 3 of grade 4 on a scale of 1, 2, 3, 4, 1 of grade 3 and 2 of grade 2. Six showed no improvement and in 2 the condition was definitely worse. When improvement occurred it was apt to be dramatic. One patient previously given chemotherapy and fever energetically without result was given 1,200,000 units in eight days. He was relieved of photophobia by the third day and returned to work a week after penicillin for the first time in many months. He has remained well, improvement continuing up to the stage of stationary residue. Another improved grade 4 and one hundred and four days after penicillin flared and recovered again without further treatment. A persistently seronegative congenital syphilitic patient with characteristic stigmas made no response and in fact became worse under 1,200,000 units. One of McDermott's patients, a fever failure, received a total of 4,845,000 units in two courses without results. Thomas secured improvement in a case on 4,000,000 units over twenty-five days, 20,000 units every three hours. Moore has excellent serial color photographs of a favorable case. One of his cases likewise improved on 3,970,000 units in twenty-one days, observed for one hundred and fifty-nine days.

OTHER EYE LESIONS

Two cases of optic neuritis on 2,000,000 and 3,000,000 units both showed improvement; O'Leary's case improved 100 per cent on retreatment. Two cases of iritis improved 100 per cent, but 1 relapsed and required an iridectomy for beginning glaucoma, after failing to respond to retreatment.

EIGHTH NERVE DEAFNESS

Eighth nerve deafness, beginning in a woman of 31 with undoubted stigmas of congenital infection, improved somewhat though not definitely on 1,200,000 units. There was a suggestion of Herxheimer-like drop in hearing at the outset followed by improvement, but the interpretations are complex. Two other cases, already far advanced, failed to improve.

MISCELLANEOUS CASES

A scattered group of cases, on which information is incomplete, includes bone-liver combinations, hepatosplenic complexes, seroresistance (Wassermann fastness) already discussed, Charcot hip and gangrenous balanitis in a syphilitic patient. The Charcot hip did not improve, and a suspected Charcot ankle is developing since penicillin. The gangrenous balanitis healed with the loss of less than a third of the corpus spongiosum on 300,000 units at about the rate to be expected of a late syphilid. The patient became seronegative. The livers of 2 patients undoubtedly enlarged (late cases) after treatment and the blood bilirubin increased in 1, then subsided.

REACTIONS TO PENICILLIN

Penicillin is not a reactionless drug. The disposition to pour it about like water in syphilis may lead to serious trouble, especially from therapeutic shock and possibly also from therapeutic paradoxical effects. The former is important under the usual rule that an active syphilitic process in a vital structure may be gravely and even fatally damaged by the impact of a large dose or series of doses at the start of treatment. Most Herxheimer effects, however, seem controllable by reduction in dosage for the first twenty-four to forty-eight hours of an eight day series without loss of ultimate effect. There is some question whether there are not delayed Herxheimer effects such as are suggested by spinal fluid and blood serologic curves and the initially unfavorable but ultimately favorable course of some lesions (eye, nervous system, for example).

Of 182 cases 43 (24 per cent) had reported reactions interpretable as Herxheimer or therapeutic shock effects. Of these 23 were fever, highest 105.5 F. The blood reagin titer increased definitely and then subsided in 7 cases. In 4 Pennsylvania cases symptoms interpreted as Herxheimer effects in the nervous system included transverse myelitic symptoms in 1 case, jacksonian convulsions lasting twelve hours in another, exacerbation of lightning pains, mania and hallucinations.

Other reactions to penicillin included urticaria (2 cases) and 1 each of "allergic reaction," "id" reaction, burning of the skin, profuse sweating and phlebitis (intravenous injection). Two patients had sharp gastrointestinal reactions.

SUMMARY

From a material of 182 cases of late syphilis preponderantly neurosyphilis (122 cases) and including benign gummatous syphilis, ocular and other forms of syphilis and late congenital syphilis, observed from eight to two hundred and fourteen days after the penicillin therapy was begun on a wide range of time-dosage schedules, the following tentative observations are summarized:

1. The lesions of benign gummatous syphilis of skin and bones heal under a dosage of approximately 300,000 units in twelve to forty-six days.

2. Irrespective of the system used, and in all types of syphilis, pencillin causes reduction of syphilitic reagin titer in the blood in from 50 to 60 per cent of late cases. An initial "Herxheimer"-like or provocative rise is observed in about 20 per cent of cases. Only 5 seroresistant cases were treated, 1 made negative, 4 improved.

3. The abnormal spinal fluid in neurosyphilis is improved in 74 per cent to some degree, definitely in

33 per cent. The commonest change is a drop in cell count and total protein (grade 2 improvement on a scale of 5) occurring in 67 per cent of cases. One spinal fluid was rendered normal within the observation period. All four fluid findings improved in 25 per cent of the cases of asymptomatic neurosyphilis, 10 per cent in paresis and taboparesis.

4. Symptoms improved in neurosyphilis as follows: Simple demented paresis: In 30 cases on which data were adequate for classification, 80 per cent improved to some degree; nearly half improved 50 per cent or more, including 8 who improved 75 per cent and 1 restored to normal. Deteriorated paresis: Two of 10 improved 75 per cent, 1 50 per cent, 7 no change. Tabes dorsalis: One fifth of 14 cases improved 50 per cent or more. Of 7 with lightning pains, 2 were completely relieved, 1 improved 50 per cent, 2 improved 25 per cent, 1 unchanged and 1 worse. Of 7 cases of primary (?) optic atrophy, mostly advanced none were made worse, 1 improved. In meningovascular neurosyphilis 40 per cent improved 50 to 75 per cent.

5. Two attempts at statistical evaluation were made: One, of the influences of smaller dose as contrasted with larger dose treatment and the other, of the response under penicillin of spinal fluids with low as contrasted with relatively high cell counts, because of small numbers of cases and unavoidable disparities in observation period, cannot be accepted as beyond challenge. They suggest respectively that in late syphilis, especially neurosyphilis, smaller doses, if not grossly inadequate, have good effects which may perhaps be improved by repetition, as compared with the effects of initial larger dosage, the effect being due perhaps to stimulation or utilization of the patient's resistance and defensive responses. The figures on response in relation to cell count suggest that moderate and high cell count cases tend to react somewhat better than cases giving low cell counts.

6. Previous treatment for syphilis by older methods in neurosyphilis, including fever therapy, does not appear to prepare patients for superior results with penicillin.

7. In late congenital syphilis, interstitial keratitis presents rather equivocal though at times dramatically favorable results, not as yet interpretable in relation to a time-dosage system. Of 14 cases 6 improved, 3 to 100 per cent, 1 to 75 per cent, 2 to 50 per cent. Two were made definitely worse.

8. Optic neuritis included 2 cases, both improved, the second 100 per cent on retreatment. Two cases of iritis improved 100 per cent at the start, but 1 relapsed and did not respond to retreatment (glaucoma).

9. Two cases of eighth nerve deafness gave equivocal results.

10. Of miscellaneous cases, Charcot joint was unaffected (a new one developing); gangrenous balanitis was cured by low dosage.

11. Therapeutic shock (Herxheimer) effects are undoubted, may be serious in late syphilis and should be guarded against by reduced dosage during the first twenty-four to forty-eight hours. Severe cerebral and cord symptoms may develop in neurosyphilis.

Reactions to penicillin as such are few and not serious, urticaria, itching, allergic skin reactions and a sharp gastrointestinal reaction following the course.

12. It is suggested that, because of the great difficulty in developing uniform records for statistical or punch machine evaluation in late syphilis, further investigation of its behavior under penicillin therapy be committed to individual competent investigators who can apply the principles of uniformity of treatment and record evaluation simultaneously with appropriate individualization of the particular case. The durability of the good effects thus far observed, the possibility of complications from induced allergic response and disturbance of the immunity balance of the individual in latent and late syphilis remain to be explored by larger experience and longer periods of observation.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. MAHONEY, ARNOLD AND STERNER AND MESSRS. HARRIS AND ZWALLY, OF DRS. MOORE AND MAHONEY, COMMANDER SCHWARTZ, LIEUTENANT COLONEL STERNBERG AND DR. WOOD, AND OF DR. STOKES, LIEUTENANT COLONEL STERNBERG, COMMANDER SCHWARTZ AND DRS. MAHONEY, MOORE AND WOOD

LIEUTENANT COMMANDER E. E. BARKSDALE, MC-V(S), U.S.N.R.: As of June 1, 1944 we have treated 161 cases of syphilis with penicillin. Twenty-nine were seronegative, dark field positive, primary syphilis, clinically cured and are still seronegative to date. Eighty were seropositive, dark field positive primaries. Of this group 2 relapsed within approximately three weeks after treatment was started. The lesions recurred in the same location and again became dark field positive. One of this group healed, becoming seronegative, and then acquired a new infection with a dark field positive chancre in a different location from the previous one. We have treated 31 cases of secondary syphilis. All the cases were treated on a dosage of 1.2 million units intramuscularly, i. e. 20,000 units every three hours for sixty injections. By determining quantitative blood penicillin levels on these patients treated with intramuscular injections every three hours, we found that it was impossible to maintain a constant penicillin level, and indeed for one third of the time there was no penicillin detected in the blood by the test used. This made us think that the continuous intravenous drip method might be the procedure of choice. To date we have treated 11 cases of syphilis by this method, giving a total of 2,080,000 units of penicillin in nine days. With this we were able to maintain a more or less constant blood penicillin level approximately ten times higher than that which could be obtained by the intramuscular route. We have had no relapses, no central nervous system involvement and no case has retained a positive serologic reaction as yet beyond the fourteenth week. To date we have treated 7 cases of syphilis with the usual routine of fever therapy but substituting for mapharsen 60,000 units of penicillin intravenously each time they were in the fever cabinet. In addition and over the same period of time we gave each patient 20,000 units of penicillin intramuscularly every three hours until a total of 3½ to 4 million units had been given. It is our impression that this method is superior to the one which we had formerly used. I am of the opinion at the present time that penicillin is the best drug we have ever had for the treatment of syphilis. I think that it is possible that the intravenous method of administration may be superior. We have had 1 case of primary syphilis treated intramuscularly with 1.2 million units, which ended fatally ten days after the completion of treatment, of a subdural hemorrhage which was not related to either the syphilis or the treatment. Pathologic examination of body tissues with special stains failed to reveal any spirochetes. At autopsy therefore this 1 case within ten days after treatment gave no pathologic evidence of syphilis.

Captain William Leifer, M. C., A. U. S.: The experience at Fort Bragg now comprises 116 patients treated for syphilis with penicillin. One hundred received 1,200,000 units and 16 received 2,400,000 units in seven and one-half days (technic sixty consecutive intramuscular injections of 20,000 or 40,000 units at three hour intervals). Reactions were infrequent and inconsequential: there were 3 instances of urticaria, 1 of erythema multiforme, 2 of generalized pruritus and 7 of herpes simplex. Focal and systemic Herxheimer reactions appeared on the first day of treatment in 87 per cent of the patients. Only those who received 1,200,000 units and who have been followed at least three months are being reported. Ten patients began treatment in the seronegative primary phase and 12 in the seropositive primary phase. Four have been observed over six months, of whom 3 are seronegative, while the fourth has a doubtful Kahn reaction. All 4 had negative spinal fluids at six months. The remaining 18 patients have been followed from three to six months, and all but 1 are seronegative. Thus, 20 of the 22 cases of primary syphilis have achieved or maintained seronegativity. Twenty-five patients began treatment in the secondary stage of syphilis. Two have exceeded six months of observation; 1 is seronegative and the other has a doubtful Kahn reaction. Both had negative spinal fluids at six months. The remaining 23 patients have been followed between three and six months; of these, 11 are seronegative, 9 still have some degree of positivity of the blood and 3 are definitive failures. Two failures appeared as neurologic relapses (1 with monoplegia, the other with acute syphilitic meningitis) with strongly positive spinal fluid; the spinal fluid had been negative in both of these immediately before administration of penicillin. The third failure was a cutaneous and serologic relapse. Thus, of 25 cases of secondary syphilis 12 are seronegative, 10 are still seropositive and 3 are outright failures. It would seem best to use higher doses than might now appear necessary in the treatment of syphilis. The future may reveal the need not only for an increase dosage but also for prolongation of the treatment period beyond the present seven and one-half days. Thus far the results have been extremely encouraging, but mass treatment of syphilis with penicillin should be delayed until the optimal treatment schedule is determined.

Commander Frank A. Ellis, Corpus Christi, Texas: I should like to give you some of the highlights of the experience with penicillin starting in New Zealand in Wellington and extending up to Corpus Christi. An enlisted man with acute infectious jaundice, after being in the hospital five days, developed an acute gonococcic urethritis. His icterus index was 45, and we gave him penicillin; it cured his gonorrhea, and his icterus index was brought down to 0.5. Penicillin might cure acute jaundice or acute infectious jaundice, as we designate it in the Navy. Our results in probably 450 cases of acute gonococcic urethritis have been 100 per cent effective, with this exception: We had 2 cases in which acute epididymitis developed three days after administration of 100,000 units of penicillin. On those we immediately repeated the therapy and gave them 200,000 units until the smears, urine culture and prostatic cultures were negative. My impression is that it certainly shortens the course of acute epididymitis. Our results have been most disappointing in penicillin therapy for nonspecific urethritis. With syphilis I have had no experience whatever except this, that I want to caution you about intraurethral chancre being masked in acute gonorrhea. If patients are given 100,000 units, the dosage will be inadequate.

Colonel Udo J. Wile, U. S. P. H. S.: It is too much to expect of penicillin at this time more than has been graphically told by the authors. We should accept these facts with the possibility that in time the organisms may elaborate for themselves a certain degree of resistance to penicillin. When we can speak in terms of thousands instead of terms of hundreds, we may have more relapses and more recurrences and possibly more reactions. It is, however, a great relief to those of us who have for years felt that we were using dangerous drugs in the treatment of syphilis to find something at least that departs from heavy metals that gives a high index of therapeutic effectiveness and apparently a low toxicity.

Dr. Joseph E. Moore, Baltimore: I close on the same restrained note of optimism which has been voiced to you here. I don't think that penicillin is ready for mass application. I do feel that our attitude ought to be one of hopefulness, but with complete understanding that we are still in the process of learning how to use the drug. We don't know yet, and it is going to be some time before we are sure.

PENICILLIN THERAPY OF GONORRHEA IN MEN

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Penicillin inhibits the growth of bacteria; some authorities maintain that it is an extremely powerful bactericidal agent also. It is nontoxic in various amounts necessary for therapeutic purposes.

This report is a continuation and combination of two previous preliminary reports published by Drs. Mahoney, Van Slyke and Arnold at the U. S. Marine Hospital, Staten Island, N. Y. This report is not made to establish the efficacy of penicillin in the treatment of gonorrhea but to try to determine the proper and minimal dosage to obtain the necessary cure.

Numerous articles have appeared on treatment with penicillin. In the first one, by Herrell, Cook and Thompson,[1] 5 cases were reported in which the continuous intravenous drip method was employed with favorable results. In the second and third articles, by

Details of Treatment

Group	Number Treated	Number Cured	Number Failed	Number of Doses	Units per Dose	Total Dosage
A	75	74	1	16	10,000	160,000
B	23	23	0	5	20,000	100,000
C	25	21	4	4	25,000	100,000
D	25	24	1	5	15,000	75,000
E	21	16	5	5	10,000	50,000
F	32	32	0	6	20,000	120,000
G	24	23	1	6	18,750	112,500
H	16	16	0	6	16,666	100,000
I	387	377	10	6	20,000 (1st and 6th 20,000; 4 of 10,000)	80,000
J	39	38	1	6	10,833	65,000
K	86	80	6	6	10,000	60,000

Dr. Mahoney and his associates[2] and by Van Slyke, Arnold and Buchholtz,[3] the intramuscular route was employed. The results will be correlated and included in the present series of cases.

The patients included in this report were all young, healthy men of the Merchant Marine and enlisted personnel of the Coast Guard, their chief disability being gonorrheal urethritis. All had failed previously to obtain a cure following some form of sulfonamide therapy, the amounts varying anywhere from 20 to 500 Gm. during the course of treatment. The diagnosis was based on positive spread and confirmed by positive culture for gonococci.

Penicillin may be administered by repeated intravenous injections, by continuous intravenous drip, or by the intramuscular route. When administered by intramuscular injection it is usually given in a concentration of 5,000 units or more per cubic centimeter, injections being made at short intervals (one to three hours). Freshly prepared solutions of penicillin are preferred.

Our initial trial was by the intravenous route on patients with gonorrhea resistant to the sulfonamides. Five patients, each receiving a total of 125,000 units of penicillin, were treated. This amount was divided into five injections of 25,000 units dissolved in 10 cc. of fresh sterile distilled water given every four hours. The result was three cures and two failures. We did not consider this result to be satisfactory. We found that the penicillin is too rapidly excreted when given by vein.

It was then decided to use the intramuscular route. The result of this method was given in a report by Dr. Van Slyke [2] and the Venereal Disease Research Laboratory in a series of 75 cases studied. A total dosage of 160,000 units intramuscularly was given over a treatment period of forty-five hours. The dosage consisted of 10,000 units every three hours of sixteen injections (day and night). Seventy-four patients responded satisfactorily; 1 was a therapeutic failure. No serious toxic reaction of any kind occurred.

A reduction in the dose-time ratio was then used. The result of this method will be seen in the accompanying table.

The sum total of cases treated with the various dosages, as shown in the table, was 753, of which 29 were failures, a percentage of 4.

The following groups are essential for discussion. Group A: Of 75 patients treated, 74 were cured and there was 1 failure. The result is good, but the period of treatment was too long, and too many injections were required (one every three hours, day and night, for two days). In group B there were 23 patients cured out of 23 treated. Group F showed the same result; out of 32 patients treated there were 32 cured. The latter was an excellent group with satisfactory dosage and a sufficient number of doses. Group H showed a good result, with 16 patients treated and 16 cures obtained. In group I 387 patients were treated and 377 responded satisfactorily. This group of patients received 20,000 units of penicillin as the initial dose and also as the last and sixth dose. The dosage in between consisted of 10,000 units for four injections. When the medication is limited and the number of patients is large, this appears to be the most satisfactory method of treatment at the present time.

It appears that the time factor has been satisfactorily established as a three hour interval between doses. The number of doses necessary for results is five to six injections at least. The intramuscular route is the most satisfactory because it is simple, easy to give, and absorption is slower than with the intravenous route. As regards toxicity, there was no evidence of any immediate or delayed reaction noticeable from the drug. The strains of gonococcus are very sensitive to penicillin. There is no difference with regard to response between untreated patients and those who previously failed to respond to sulfonamides.

COMMENT

The clinical study based on 753 patients treated with penicillin indicates that the strains of gonococci are very sensitive to this drug. Groups B, F and H showed no failures. This appears to indicate that a total of 100,000 units or more is necessary to produce a cure. It also indicates that five to six injections are necessary. In group I the total dosage of only 80,000 units was due to limitation of the drug. The results are excellent in that of 387 patients treated 377 were cured, with 10 failures, the result showing only 3 per cent failures.

The patients treated unsuccessfully were eventually cured as follows: Four were treated with a combination of chemotherapy plus fever therapy [4] (i. e. 6 Gm. of sulfathiazole followed by fever therapy, with a temperature of 106 F. for six hours). The sulfathiazole was given in doses of 1.0 Gm. every four hours for six doses, and then within two hours fever therapy was employed. Five patients responded after a second course of penicillin, in accordance with group F. One patient required a third course of penicillin, a total of 175,000 units divided into 25,000 units given every three hours intramuscularly for seven injections.

The dosage necessary to produce a cure is 20,000 units per dose for six injections, making a total of 120,000 units. This has been shown in 42 cases with no failures.

The next best group is group I, in which 381 patients were treated as follows: 20,000 units for the first dose, then 10,000 units for the next four doses and finally 20,000 units for the sixth and last dose a total of 80,000 units. The result showed 377 cures and 10 failures, a little over 2 per cent of failures.

As regards toxicity, there was no evidence of any immediate or delayed reaction noticeable from the drug.

notes

From the U. S. Marine Hospital, medical director, William Y. Hollingsworth, medical officer in charge.

1. Herrell, W. E.; Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide-Resistant Gonorrheal Infections, J. A. M. A. **122**: 289 (May 29) 1943.

2. Mahoney, J. F.; Ferguson, C.; Buchholtz, M., and Van Slyke, C.: The Use of Penicillin Sodium in the Treatment of Sulfonamide-Resistant Gonorrhea in Men, Am. J. Syph., Gonor. & Ven. Dis. **27**: 525 (Sept.) 1943.

3. Van Slyke, C. J.; Arnold, R. C., and Buchholtz, M.: Penicillin Therapy in Sulfonamide-Resistant Gonorrhea in Men, Am. J. Pub. Health **33**: 1392 (Dec.) 1943.

PENICILLIN TREATMENT OF SULFONAMIDE RESISTANT GONOCOCCIC INFECTIONS

IN FEMALE PATIENTS

PRELIMINARY REPORT

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Several publications,[1] have already appeared on the subject of penicillin treatment of sulfonamide resistant gonococcic infections. These reports, however, dealt exclusively with infections in the male. The present report deals with the result of penicillin treatment of sulfonamide resistant gonococcic infections in 44 women.

All of the women included in this study were hospitalized for the purpose of penicillin treatment in the gynecologic service of Bellevue Hospital. After an initial follow-up of at least five clinical and bacteriologic examinations the patients were discharged with instructions to report at the clinic of the Gonococcus Research Unit, Department of Health, City of New York, for further observation.

CLINICAL MATERIAL

Forty-two of the 44 cases had failed to respond to at least 2 courses of 20 Gm. of sulfathiazole. The remaining 2 women had exhibited a definite hypersensitivity to sulfonamide and therefore were given penicillin treatment.

The presence of gonococcic infection was verified by smears and cultures performed at the laboratory of this unit. Infection of the cervix alone was reported in 12 patients, of the urethra alone in 1 and a concurrent infection of the urethra and cervix in the remaining 31. Involvement of the adnexa was found in 15 patients. Four of the women were pregnant. The average duration of infection prior to penicillin treatment was 92.5 days (maximum nine months, minimum twenty-one days).

TREATMENT

Each 10,000 Oxford units of penicillin was dissolved in 2 cc. of sterile isotonic solution or distilled water. The penicillin was injected intramuscularly in the gluteal region. Injections were repeated at three hour intervals.

The laboratory work was aided by a grant from the United States Public Health Service.

From the Gonococcus Research, Department of Health, City of New York, and the Obstetrical and Gynecological Service (Third Surgical Division), Bellevue Hospital, and from the Department of Obstetrics and Gynecology, New York University College of Medicine.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

1. Herrell, W. E.; Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289 (May 29) 1943. Mahoney, J. F.; Ferguson, Charles; Buchholtz, M., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide Resistant Gonorrhea in Men, Am. J. Syph., Gonor. & Ven. Dis. **27**: 525, 1943. Van Slyke, C. J.; Arnold, R. C., and Buchholtz, M.: Penicillin Therapy in Sulfonamide Resistant Gonorrhea in Men, Am. J. Pub. Health **33**: 1392, 1943.

DOSAGE

The accompanying table represents the number of patients treated and the amounts of each single dose and the total dosage of penicillin administered at three hour intervals.

RESULTS OF THERAPY

All 44 patients were apparently cured by penicillin treatment. In 1 case, however, a relapse occurred on the second day following the termination of therapy. This patient had received only 50,000 Oxford units of penicillin; she became bacteriologically negative after subsequent treatment with an additional 100,000 Oxford units of penicillin.

Following penicillin treatment, daily clinical and bacteriologic examinations were performed. All the patients showed a reversal of their initial bacteriologic findings from positive to negative within twenty hours after the termination of penicillin therapy. Follow-up at Bellevue Hospital was continued for an average of 7.2 days, and an average of 5.8 bacteriologic examinations were performed on each patient. The additional average follow-up period in the clinic of the Research Unit was 38.4 days, and an average of 3.6 examinations were performed up to date. All the patients followed up (37) remained bacteriologically negative throughout this period.

No significant changes in the amount and character of the cervical discharge after penicillin treatment were observed. However, the urethral discharge in a number of cases decreased or disappeared completely. Among the 15 patients with adnexal involvement the inflammation subsided in 7 and remained the same in 5 others. In the remaining 3 an exacerbation of the adnexal involvement was observed following the use of penicillin. One of the 24 patients without any adnexal disease prior to penicillin treatment developed salpingitis following therapy.

The course of the pregnancy in 4 patients was affected in no way by the penicillin treatment.

Eleven of the 44 patients studied suffered from a concurrent infection with Trichomonas vaginalis, which remained entirely unaffected by this type of treatment.

In addition to the penicillin treatment of women there was 1 case of sulfonamide resistant gonococcic vaginitis in a child aged 5 years, who was given four single doses of 10,000 Oxford units of penicillin at three hour intervals (Children's Medical Service of Bellevue Hospital, Dr. James L. Wilson, director). This child promptly became negative and remained negative during a follow-up period of twenty-five days.

TOXICITY

The administration of penicillin in the recorded dosage produced no toxic effects. The only complaint mentioned by nearly all the patients was that following the penicillin injection numbness or pain radiating from the site of injection in the gluteal region down to the thigh or to the ankle occurred. These symptoms lasted for only a few minutes.

COMMENT

Reviewing the results obtained thus far, it appears that a minimum total dosage of 75,000 Oxford units of penicillin is satisfactory in the treatment of sulfonamide resistant gonococcic infection in the adult female.

If this observation is confirmed further, it will be possible to control sulfonamide resistant gonorrhea by one day treatment of ambulatory patients. The single relapse among a group of 9 women, each of whom had received a total dosage of 50,000 Oxford units of penicillin, points to a varying individual susceptibility to this agent. Smaller dosage of penicillin may prove adequate in many cases. This difference in the degree of susceptibility to the therapeutic action of penicillin has also manifested itself in in vitro experiments carried out by this unit.[2]

Dosage of Penicillin Administered in Various Groups of Sulfonamide Resistant Gonococcic Infections in 44 Adult Female Patients

Group	Number of Patients	Single Dose	Number of Injections	Total Dosage
1	12	20,000 Oxford units	5 doses	100,000 O. U.
2	10	25,000 Oxford units	4 doses	100,000 O. U.
3	12	25,000 Oxford units	3 doses	75,000 O. U.
4	1	20,000 Oxford units	3 doses	60,000 O. U.
5	8	25,000 Oxford units	2 doses	50,000 O. U.
	1*	25,000 Oxford units	2 doses	50,000 O. U.
		25,000 Oxford units	4 doses	100,000 O. U.

* Only failure after total dosage of 50,000 Oxford units; responded to an additional total amount of 100,000 Oxford units.

SUMMARY AND CONCLUSIONS

1. Forty-two adult female gonorrheal patients who did not respond to at least two courses of sulfathiazole were treated with various amounts of penicillin. Two additional infected patients were also given penicillin because they were sensitive to sulfonamides.

2. Forty-three women of the total of 44 promptly became bacteriologically negative after treatment with penicillin and remained negative during the follow-up period.

3. Only 1 of a group of 9 patients showed a relapse following a total dosage of 50,000 Oxford units of penicillin; she responded to an additional total amount of 100,000 Oxford units of penicillin.

4. The bacteriologic reversal from gonococcus positive to negative took place as a rule within twelve hours following the termination of therapy.

5. A total dosage of 75,000 Oxford units of penicillin appears to be satisfactory in the treatment of sulfonamide resistant gonorrhea in the adult female. This therapy may be completed within a period of six hours.

6. A child aged 5 years with a sulfonamide resistant gonococcic vaginitis became bacteriologically negative after a total dosage of 40,000 Oxford units of penicillin.

7. No toxic effects due to the administration of penicillin were observed.

Room 1020, 125 Worth Street.

2. Cohn, A., and Seijo, I.: The in Vitro Effect of Penicillin on Sulfonamide Resistant and Sulfonamide Susceptible Strains of Gonococci, to be published.

THE TREATMENT OF GONORRHEAL URETHRITIS

WITH SULFONAMIDES AND PENICILLIN COMBINED

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When penicillin became available at the U. S. Naval Hospital, Bainbridge, Md., in October 1943, a large number of patients with sulfonamide resistant gonorrheal urethritis were under treatment. Most of them had been treated for long periods, almost all for more than forty days, a fairly large number for more than sixty days, and one man had been on the sick list one hundred and twenty-eight days. Treatment had consisted in repeated courses of sulfathiazole and sulfadiazine (table 1), in most instances with the addition of standard types of local therapy. The penicillin sodium was procured from two nationally known pharmaceutical firms. At first the dosage recommended by Keefer and his associates,[1] 160,000 Oxford units at the rate of 10,000 units every three hours, was injected into the muscle. It soon became apparent, however, not only that penicillin was brilliantly efficacious but that its action was so rapid that in all the cases clinical and bacteriologic cure resulted within twenty-four hours. In many the urethral discharge and all symptoms ceased within nine hours. In the meantime Turner and Sternberg[2] suggested that 50,000 Oxford units would probably be efficacious in gonorrheal urethritis, although they predicted, apparently as the result of experience, that 10 to 20 per cent failures might be expected with such dosage. Those considerations, together with the limited availability of the drug and the need to conserve it, led us progressively to decrease the dosage, until finally a series of 73 sulfonamide resistant cases were treated with 50,000 Oxford units of penicillin each (table 1, group B). There was but 1 failure. As a result, however, of conversations with Dr. C. S. Keefer and with Capt. W. W. Hall of the Medical Corps, U. S. Navy, it was suspected that the striking success with 50,000 units obtained in that series might be more fortuitous than real. They pointed out that the assay of penicillin is as yet subject to such

From the U. S. Naval Hospital, Bainbridge, Md.

The authors were assisted by Lieut. H. W. Savage (MC), U. S. N. R., and Ensign Elma Krumwiede, Women's Reserve, U. S. N. R.

Since this article was prepared the authors have treated 71 additional cases with combined sulfonamide-penicillin. The results were in all respects similar to those described and do not differ statistically from those of table 2.

1. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections, J. A. M. A. **122**: 1217 (Aug. 28) 1943.

2. Turner, T. B., and Sternberg, T. H.: Management of the Venereal Diseases in the Army, J. A. M. A. **124**: 133 (Jan. 15) 1944.

3. Foster, J. W., and Woodruff, H. B.: Microbiological Aspects of Penicillin: I. Methods of Assay, J. Bact. **46**: 187 (Aug.) 1943; Improvements in the Cup Assay for Penicillin, J. Biol. Chem. **148**: 723 (June) 1943.

limitations that in using doses of 50,000 units the variation of actual dosage administered may range from as little as 30,000 units to as much as 70,000 units. Foster and Woodruff [3] have written of the limitations and difficulties in performing accurate assay of penicillin. Moreover, a subsequent report from the Army [4] indicated that when 50,000 units of penicillin alone was used to treat sulfonamide resistant gonorrheal urethritis the failures were in excess of 15 per cent. In the meantime Rammelkamp and Keefer [5] had suggested that a combination of a sulfonamide compound with penicillin might prove more effective than either drug alone in staphylococcic infections. In their preliminary observations they had observed that "the addition of small amounts of penicillin, which in itself displays no killing effect against staphylococci, will enhance the antistaphylococcal effect of sulfathiazole in whole defibrinated blood." It was desirable, therefore, in view of these considerations to investigate the effect of a combination of sulfathiazole and small doses of penicillin on acute gonorrheal urethritis. Table 2 summarizes the results of that investigation.

METHODS

The criteria of diagnosis of gonorrheal urethritis were a history of exposure, when it could be obtained, the presence of a purulent urethral discharge and demonstration of Neisseria gonorrhoeae in smears. Criteria of cure were disappearance of symptoms and of urethral discharge, and failure to find and to culture Neisseria gonorrhoeae from material obtained by prostatic massage between the fourth and fifth days after the completion of treatment, and again between the tenth and fifteenth days. The culture medium employed was a beef extract agar base containing bactotryptose or neopeptone with 0.03 per cent dextrose and 5 per cent sodium chloride with 10 cc. of a 0.5 per cent solution of paraaminobenzoic acid added to each liter of medium.

The treatment of patients listed in table 1 consisted in the administration of penicillin as shown. The treatment of all patients listed in table 2 consisted in the following: On the first day 8 Gm. of sulfathiazole was given orally in four divided doses; on the second day 4 Gm. of sulfathiazole in divided doses was given with the concomitant administration of 50,000 Oxford units of penicillin at the rate of 10,000 units (5,000 units per cubic centimeter) every three hours in the muscle. Intramuscular injections at the rate of 10,000 units every three hours were used as a result of the studies of Rammelkamp and Keefer,[6] of Dawson, Meyer and Chaffee [7] and because our previous experience had indicated that that rate was highly efficacious.

TABLE 1.—*Patients with Sulfonamide Resistant Gonorrheal Urethritis Treated with Penicillin*

Patients	Total Penicillin Units	Concentration per Cc., Units	Units per Dose	Frequency
Group A*				
4	160,000	5,000	10,000	3 hours
17	150,000	5,000	10,000	3 hours
6	145,000	5,000	10,000	3 hours
1	140,000	5,000	10,000	3 hours
2	130,000	5,000	10,000	3 hours
34	160,000	5,000	20,000	3 hours
39	160,000	5,000	20,000	4 hours
3	80,000	5,000	20,000	4 hours
106				
Group B †				
69	50,000	5,000	10,000	2 hours
4	50,000	5,000	5,000	1 hour

* Average dose of sulfonamide prior to beginning penicillin, 52.3 Gm. ranging from 16 to 100 Gm.
† Average dose of sulfonamide prior to beginning penicillin, 24.7 Gm. ranging from 8 to 56 Gm.

TABLE 2.—*Patients with Gonorrheal Urethritis Treated with Sulfathiazole (12 Gm.) and Penicillin (50,000 Oxford Units) Combined*

	Cured	Failed	Total	Per Cent Failed
White				
Group A *	25	2	27	7.40
Group B †	39	4	43	9.30
Total white	64	6	70	8.57
Negro				
Group C ‡	112	2	114	1.75
Group D §	46	2	48	4.16
Total Negro	158	4	162	2.47
Total all cases	222	10	232	4.31

* White recruits.
† White men with acute untreated disease.
‡ Negro recruits.
§ Negro men with acute untreated disease.

The data from the study are presented in the accompanying tables. Our results with the use of penicillin in doses of 80,000 or more Oxford units in sulfonamide resistant gonorrheal urethritis are in accord with those obtained by others.[8] In almost all cases in which such doses were administered the symptoms and urethral discharge cleared and bacteriologic cure resulted within twenty-four hours or less. In a few a slight mucoid discharge persisted for a few days.

The results in sulfonamide resistant gonorrhea in patients who received only 50,000 units of penicillin (table 1, group B) were unexpected in that there were no failures. The series (73 cases) seems somewhat large to be accounted for by mere chance. Because, as already indicated, the error of the assay of penicillin may be considerable when dealing with small amounts, it might be supposed that the patients actually received considerably more than 50,000 units, but against such a supposition is the fact that several different batches of the drug obtained from two different pharmaceutical firms were used in treating those patients, and it is unlikely that an error would always have been in the same direction. Although the aforementioned factors may have played a role, we are of the opinion that the excellent results obtained with the combined drugs occurred because the drugs actually enchanced the efficacy of each other. Enhanced clinical effectiveness in the treatment of staphylococcic infections by using sulfonamide compounds and penicillin combined was predicted by Rammelkamp and Keefer [5] as a result

4. Hall, W. W., Capt., M. C. U. S. Navy: Personal communication to the authors.
5. Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus, J. Clin. Investigation **22**: 425 (May) 1943.

of their experimental observations. Further support of that idea will become evident when the results listed in table 2 are studied. Clinically the only difference between the patients receiving 50,000 units and those receiving the larger doses was that in the former the urethral discharge abated somewhat more slowly, usually over a period of two to three days, but the patients were bacteriologically cured just as promptly.

Group A of table 2 was composed of white men whose disease was discovered in the receiving line for recruits. Because the histories were usually unreliable, estimation of the duration of their disease or of previous treatment was not attempted. In many the disease had probably existed for prolonged periods and had received considerable treatment; in others it was probably of fairly recent origin, frequently being the result of a "last fling" just prior to the induction into the Navy. Group B of table 2 consisted of white men who had been in naval service for at least six weeks. Because such men report promptly to the sick bay, it is safe to assume that all cases were of recent origin and that they had not received previous treatment. Table 2, group C, is similar to group A except that the patients were Negroes; group D corresponds to group B with the same exception.

That gonorrhea in Negroes is more amenable to treatment than it is in white men has long been the belief of physicians. Turner and Sternberg [2] have recently shown a striking difference between the races in the effectiveness of treatment with sulfonamides. The results given in table 2 show a similar difference in the racial responses to treatment with penicillin and sulfonamides combined.

The results shown in table 2 also support the idea that sulfonamides enhance the effectiveness of penicillin. In an analysis of almost 7,000 cases Turner and Sternberg [2] showed that from 25 to 35 per cent of white men with gonorrheal urethritis fail to respond to one course of treatment with sulfonamides and that approximately 10 per cent of Negroes fail to respond. It has also been demonstrated that treatment of the disease with 50,000 units of penicillin alone results in upward of 15 per cent failures.[4] In contrast, the data of table 2 show that with the combined use of a moderate amount of sulfathiazole with 50,000 units of penicillin from one half to one third as many failures occur as result when similar amounts of the drug are used alone. Furthermore, when previous treatment with sulfonamides is followed by the combined sulfonamide-penicillin therapy the rate of cure is even greater, especially in the Negro (table 2, groups A and C). Whether or not the increased effectiveness is due to true synergism between the drugs is not clear, because, as stated, penicillin therapy is also more efficacious for patients who have received previous treatment with sulfonamides. One might, of course, assert that the greater effectiveness when the drugs are used simultaneously is due not to an additive effect or to an enhancing of one drug by the other but merely to the fact that a certain number of patients are cured by one drug while the other drug was ineffectual. From a practical standpoint, however, the important factor is that the concomitant use of moderate amounts of sulfonamides (12 Gm.) and of penicillin (50,000 units) is strikingly more effective than when either drug is used alone.

Clinically it was noteworthy that the patients treated concurrently with the drugs were cured promptly, and that except for 1 patient failure to cure was obvious within three or four days. When the treatment failed, symptoms failed to disappear, the urethral discharge abated but slightly or not at all, and smears remained positive for Neisseria gonorrhoeae. Only 1 patient, whose symptoms and discharge cleared immediately and who was bacteriologically "cured" on the seventh day, later had a recurrence of mucoid discharge from which Neisseria gonorrhoeae was cultured on the sixteenth day.

When failure to cure with the combined drugs occurred, the patients were immediately treated with 100,000 units of penicillin alone; all were promptly cured. In the entire series of cases no untoward effects from penicillin were observed.

From the military standpoint the primary consideration in treating venereal disease is saving of manpower days. From that point of view it might be considered, because of the almost complete effectiveness of treatment of uncomplicated gonorrheal urethritis with 100,000 Oxford units of penicillin, that that dose should be used in all cases. Nevertheless, in any large scale program of treatment cost must be considered, and of even more importance than cost at present is the question of availability of penicillin. The combined use of sulfonamides with small doses of penicillin has the advantages of rapid cure in a high percentage of cases, especially in the Negro, and the reduction essentially by half in the cost and the amount of the drug used. Furthermore, the ease and the promptness of recognition of the few failures which do occur when the combined treatment is used make that method from a military point of view fully as practical as the use of larger doses.

CONCLUSIONS

1. Penicillin sodium was used in the treatment of a total of 411 patients with gonorrheal urethritis.

2. A combination of moderate doses of sulfathiazole and small doses of penicillin sodium was used in the treatment of 232 patients.

3. Gonorrheal urethritis of the Negro is more susceptible to treatment with penicillin and with penicillin and sulfathiazole combined than it is in the white race.

4. Sulfathiazole and penicillin appear to enhance the effect of each other against Neisseria gonorrhoeae.

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6. Rammelkamp, C. H., and Keefer, C. S.: Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.

7. Dawson, M. H.; Hobby, G. L.; Meyer, K., and Chaffee, E.: Penicillin as a Chemotherapeutic Agent, Ann. Int. Med. **19**: 707 (Nov.) 1943.

8. Herrell, W. E.; Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289 (May 29) 1943. Mahoney, J. F.; Ferguson, C.; Buchholtz, M. S., and Van Slyke, C. J.: The Use of Penicillin Sodium in the Treatment of Sulfonamide Resistant Gonorrhea in Men, Am. J. Syph., Gonor. & Ven. Dis. **27**: 525 (Sept.) 1943. Robinson, J. N., cited in Penicillin, Foreign Letters (London), J. A. M. A. **124**: 117 (Jan. 8) 1944. Cook, E. N.; Pool, T. L., and Herrell, W. E.: Further Observations on Penicillin in Sulfonamide Resistant Gonorrhea, Proc. Staff Meet., Mayo Clin. **18**: 433 (Nov. 17) 1943. Dawson, M. H., and Hobby, G. L.: The Clinical Use of Penicillin: Observations in 100 Cases, J. A. M. A. **124**: 611 (March 4) 1944. Bloomfield, A. L.; Rantz, L. A., and Kirby, H. M. M.: The Clinical Use of Penicillin, ibid. **124**: 627 (March 4) 1944. Keefer, Blake, Marshall, Lockwood and Wood.[1]

5. The combined use of moderate amounts of sulfathiazole and of penicillin is a safe, rapid, efficient and economical method of treating gonorrheal urethritis.

NEW PENICILLIN STUDY INSTITUTED AT FORT BRAGG

Dr. Charles Rammelkamp, member of the commission on Acute Respiratory Diseases, Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, and Capt. William Leifer, M. C., Regional Hospital, Fort Bragg, North Carolina, recently spent several days in the Office of the Surgeon General conferring on the new method of administering penicillin developed by Capt. Monroe J. Romansky, M. C., at the Army Medical Center. The new technic prolongs the action of penicillin by suspending it in a mixture of 4 per cent beeswax and peanut oil. Dr. Rammelkamp will act in a consulting capacity with Dr. Leifer, who is instituting a study of the method at Fort Bragg Regional Hospital. It is believed that the new method will have important effects on the use of this agent.

J. A. M. A.
Sept. 30, 1944

PENICILLIN IN THE TREATMENT OF OPHTHALMIA NEONATORUM

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Although the sulfonamides have been of great value in the treatment of ophthalmia neonatorum, certain problems have arisen in connection with their use which seemed to justify a study of the effects of penicillin.

For several years the Illinois Department of Public Health has provided hospitalization and treatment for patients with ophthalmia neonatorum. The plan provided for immediate hospitalization of the infant in a centrally located hospital where the services of an ophthalmologist and a pediatrician were available. The infants were treated with sulfonamides orally and with irrigations locally. Although no blindness resulted in some 35 cases so treated, it was found that many infants were either intolerant to the sulfonamides or quickly became resistant. Prolonged hospitalization usually was necessary before the infant could be discharged as clinically and bacteriologically cured.

STUDY

Through the courtesy of the Committee on Chemotherapeutics and Other Agents of the National Research Council, a limited supply of penicillin was made available to study its effect on ophthalmia neonatorum.

Of the 8 cases included in this study, 5 showed gram-negative intracellular diplococci on smear and organisms giving a positive oxidase reaction and fermentations typical of gonococci on culture.

Two cases showed gram-negative intracellular diplococci on smear and oxidase positive colonies of gram-negative diplococci on culture. The organisms isolated from these two cultures failed to grow on subculture.

In 1 case the etiologic agent could not be determined, although the clinical findings were typical of ophthalmia neonatorum (case 7).

Because of the lack of precedent it was necessary at the beginning of the study to outline more or less arbitrary procedures with respect to both the dosage of penicillin and the criteria of cure.

Ten thousand units of penicillin injected intramuscularly at intervals of three hours for a total of six injections was selected as the original treatment schedule. Later this was felt to be inadequate and the dosage was adjusted individually for each case (table 1).

The criteria of cure chosen were (*a*) absence of clinical activity, (*b*) three consecutive negative smears for gram-negative intracellular diplococci and (*c*) three consecutive negative cultures for gonococci.

All patients received instillations of 0.5 per cent atropine sulfate and irrigations of sterile water during the acute clinical phase of the infection.

REPORT OF CASES

Case 1.—A Negro girl born Nov. 19, 1943, with onset November 20, admitted November 23, received a total of 39 grains (2.5 Gm.) of sulfadiazine in several courses together with 2 per cent sulfathiazole solution irrigations in both eyes between the date of admission and Jan. 8, 1944. Sulfadiazine was stopped because of persistent vomiting. Smears and cultures from both eyes were positive for gonococci on January 8, and examination revealed moderate swelling and injection of both conjunctivas with a moderate amount of purulent exudate. The corneas were normal. The patient was given 60,000 units of penicillin intramuscularly over a fifteen hour period. Definite clinical improvement was noted at the end of twenty-four hours; there was no further discharge. Both eyes were clinically normal within three days and remained so thereafter. Cultures and smears became negative on the 2d day following completion of penicillin therapy. Except for one positive culture from the right eye on the 3d day, all cultures and smears remained negative.

Case 2.—A white boy born Dec. 10, 1943, with onset December 22, admitted Jan. 10, 1944, received no treatment prior to admission other than silver nitrate prophylaxis at birth. Examination revealed moderate redness and swelling of both eyes externally. The conjunctivas were injected, and a frankly purulent discharge was present bilaterally. The corneas were clear. The patient received 60,000 units of penicillin intramuscularly during a fifteen hour period. Because of persistent clinical and laboratory findings a second course of 90,000 units (15,000 every three hours) was given on the 5th day of hospitalization but failed to effect any improvement. A short course of sodium sulfadiazine during the 13th to 16th hospital days likewise failed to elicit any response. On the 23d and 24th days a third course of penicillin was administered, 20,000 units for six doses followed by 10,000 units for six doses. The conjunctivitis continued unabated, and smears and cultures remained positive. Recovery finally occurred after the use of sulfonamides combined with foreign protein therapy.

Case 3.—A Negro boy born Jan. 12, 1944, with onset January 17, admitted January 18, had been given silver nitrate prophylaxis at birth and boric acid solution irrigations following the onset. Intense swelling and redness of both eyes externally and pronounced chemosis and injection of the palpebral conjunctivas with a frankly purulent exudate were noted on admission. No corneal involvement was found. Over a fifteen hour period 120,000 units of penicillin was administered intra-

From the Illinois Department of Public Health, Roland R. Cross, M.D., Director.
The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

muscularly. Considerable improvement occurred in both eyes within eight hours after the beginning of therapy. Chemosis and injection gradually subsided, so that both eyes appeared normal on the 6th day of hospitalization and remained so thereafter. Following treatment, smears failed to show any intracellular diplococci and all cultures were negative.

Case 4.—A white girl born Jan. 12, 1944, with onset January 27, admitted January 28, had been treated with silver nitrate at birth. On admission the right eye showed moderate swelling externally, a purulent discharge and injection and chemosis of the conjunctiva. The only involvement of the left eye consisted of slight conjunctival injection. The corneas were clear bilaterally. Initial smears and cultures revealed both gonococci and Haemophilus influenzae. The patient received 180,000 units of penicillin intramuscularly during a period of thirty-four hours (6 doses of 20,000 units followed by six doses of 10,000 units). Definite improvement was noted in nine hours, and both eyes were clinically normal on the 4th hospital day and remained so. Following the initial laboratory findings all cultures were negative for gonococci, and smears failed to show any intracellular gram-negative diplococci. Organisms resembling Haemophilus were seen in small numbers in both smears and cultures periodically throughout observation.

Case 5.—A Negro girl born Jan. 31, 1944, with onset February 3, admitted February 4, with delivery by a midwife, received no treatment prior to admission. The left eye showed external swelling and redness with a frankly purulent discharge. The left palpebral conjunctiva was injected and chemotic. There were minimal findings in the right eye. The corneas were clear bilaterally. During thirty-six hours 180,000 units of penicillin was administered intramuscularly. Improvement was noticeable after the 2d injection, and the eyes were practically normal twenty-one hours after the beginning of therapy. All cultures were negative after completion of therapy, and smears failed to show any intracellular gram-negative diplococci.

Case 6.—A Negro boy born Jan. 23, 1944, with onset January 28, admitted February 4, had been given only silver nitrate prophylaxis at birth. External redness and swelling, chemosis and purulent discharge were all present in the left eye. Minimal findings were seen in the right eye. The corneas were clear bilaterally. Initial smears were typical for gonococci in the right eye, and a culture revealed oxidase positive colonies of gram-negative diplococci which failed to grow on transplants and could not therefore be confirmed. The patient received 180,000 units of penicillin intramuscularly during a thirty-two hour period. At the time of the 4th injection definite clinical improvement was noted and by the 5th hospital day both eyes were clinically normal. All subsequent smears and cultures were negative following completion of therapy.

Case 7.—A white boy born Feb. 21, 1944, with onset February 28, admitted March 1, had received silver nitrate prophylaxis at birth and instillations of mild protein silver during the three days following onset. The right eye was moderately involved with external redness and swelling, inflammatory chemosis and a purulent discharge. Slight conjunctival findings were present in the left eye. No gonococci were found in the initial smears or cultures, but in the latter several colonies of diphtheroids were isolated. These proved to be avirulent in guinea pigs. There were no other findings which helped to determine the etiologic agent, and smears taken from the child's mother proved negative for gonococci. Penicillin was administered intramuscularly every three hours, 15,000 units in each of six doses followed by 10,000 units for fourteen doses (total 230,000 units). Specific therapy was prolonged in this case because of its failure to effect adequate improvement in clinical findings at the end of fifteen hours. At the completion of therapy moderate improvement was noted, but for the next thirteen days the condition remained static and complete recovery was not achieved. Following a short course of sodium sulfadiazine during the 17th to 19th hospital days, both eyes quickly returned to normal. Smears and cultures failed to reveal any significant organisms throughout the entire period of observation.

Table 1.—*Results of Treatment of Ophthalmia Neonatorum with Penicillin*

Case No.	Duration of Infection, Days	Etiologic Agent	Total Penicillin, Units	Beginning of Improvement, Hours	Clinical Cure, Days	Laboratory Cure, Days	Final Results
1	47	N. gonorrhoeae	60,000	24	3	9	Satisfactory
2	20	N. gonorrhoeae	330,000*	..	..	..	Unsatisfactory
3	2	N. gonorrhoeae	120,000	9	6	7	Satisfactory
4	2	N. gonorrhoeae, H. influenza (?)	180,000	9	4	6	Satisfactory
5	2	N. gonorrhoeae	180,000	6	6	24	Satisfactory
6	8	N. gonorrhoeae(?)	180,000	9	5	8	Satisfactory
7	4	(?)	230,000	..	..	..	Unsatisfactory
8	25	N. gonorrhoeae(?)	240,000	9	5	7	Satisfactory

* 60,000 units 1st day, 90,000 units 4th day, 180,000 units 22d and 23d days.

Table 2.—*Results of Smears and Cultures During and Following Penicillin Therapy*

Hospital Day	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
Admission	P	P	P	P	P	P	P	P	P	P	P*		N	N	P	P*
9th hour	N	P	P	P	..	..	D	N	D	N	D	N	N	N*	P	N
2.....	N	P	..	..	N	N	D	N	D	N	D	N	N	N	N	N
3.....	N	N	D	N	N	N	N	N	D	N	N	N	..	..	..	..
4.....	D	P	D	N	D	N	N	N	..	..	..	..	N	N	N	N
5.....	N	N	N	N	N	N	..	..	..	..	..	..	N	..	..	..
6.....	..	..	N	N	N	N	N	N	..	..	..	..	N	..	..	..
7.....	..	..	N	N	N	N	..	..	D	N	N	N	..	N	N	N
8.....	N	N	..	..	N	N	..	..	D	N	N	N	..	..	..	..
9.....	N	N	..	..	..	..	..	..	..	..	..	..	..	..	..	..
10.....	..	..	..	..	..	..	N	N	..	..	..	..	..	N	..	..
11.....	..	..	N	P	..	..	..	..	..	..	..	..	..	..	..	..
12.....	..	..	..	..	N	N	..	..	..	..	..	..	..	..	..	..
13.....	..	..	N	N	N	N	..	..	..	..	..	..	..	..	..	..
14.....	..	..	N	P	D	N	..	..	..	..	..	..	..	N-	..	..
15.....	..	..	N	N	..	..	N	N	..	..	..	..	..	N	..	..
16.....	..	..	..	..	N	N	D	N	D	..	..	..	..	..	..	..
17.....	..	..	..	..	D	N	..	..	D	..	..	..	..	..	..	..
18.....	..	..	..	..	N	N	..	..	D	..	..	..	..	..	..	..
20.....	..	..	N	P	D	N	..	..	..	..	..	..	..	..	..	..
21.....	..	..	D	P	N	N	..	..	..	..	..	..	..	..	..	..
22.....	..	..	D	P	..	..	..	..	N	..	..	..	..	..	..	..
23.....	..	..	..	..	..	..	..	..	N	..	..	..	..	..	..	..
24.....	..	..	..	..	..	..	D	..	N	N	..	..	..	..	..	..
25.....	..	..	..	..	D	N	D	..	..	..	..	..	..	..	..	..
26.....	..	..	..	..	D	N	N	N	..	..	..	..	..	..	..	..
27.....	..	..	N	N	..	..	..	..	..	..	..	..	..	..	..	..
28.....	..	..	D	N	..	..	..	..	..	..	..	..	..	..	..	..
29.....	..	..	N	P	..	..	..	..	..	..	..	..	..	..	..	..
30.....	..	..	..	..	..	..	N	N	..	..	..	..	..	..	..	..
31.....	..	..	..	..	..	..	N	N	..	..	..	..	..	..	..	..
32.....	..	..	..	..	..	..	N	N	..	..	..	..	..	..	..	..
33.....	..	..	P	N	D	..	..	..	..	..	..	..	..	..	..	..
34.....	..	..	P	N	D	..	..	..	..	..	..	..	..	..	..	..
36.....	..	..	..	..	N	N	..	..	..	..	..	..	..	..	..	..
40.....	..	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..
41.....	..	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..
57.....	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..	..
59.....	..	..	D	..	..	..	..	..	..	..	..	..	..	..	..	..
60.....	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..
62.....	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..
66.....	..	..	N	.	..	..	..	..	..	..	..	..	..	..	..	..
67.....	..	..	..	N	..	..	..	..	..	..	..	..	..	..	..	..

* Cultures showed oxidase positive colonies of gram-negative diplococci which failed to grow on subculture and therefore could not be confirmed. S = smear, C = culture, P = positive, gram-negative intracellular diplococci in smears or gonococci in confirmed cultures, D = doubtful, gram-negative extracellular diplococci in smears, N = negative smear or culture, no gonococci.

CASE 8.—A white boy born Feb. 19, 1944, with onset February 22, admitted March 17, concerning whose treatment prior to admission no information was available other than silver nitrate prophylaxis at birth, exhibited a bilateral purulent conjunctivitis at the initial examination. The conjunctival surfaces of the upper lids were granular. The corneas were not involved. Initial smears were typical for gonococci, and culture revealed oxidase positive colonies of gram-negative diplococci, which failed to grow on subcultures and could not therefore be confirmed. The patient received 20,000 units of penicillin intramuscularly every three hours for twelve doses (total 240,000 units). Definite clinical improvement was noted at the time of the 9th injection, and both eyes were clinically normal by the 5th hospital day. Smears and cultures reverted to negative on the 2d day of therapy and remained so thereafter.

COMMENT

Clinical Response.—All except 2 of the 8 cases in this series responded to therapy within twenty-four hours, as manifested by subsidence of active inflammation. Case 2 and case 7 showed some improvement during and immediately after penicillin therapy but, instead of progressing to complete recovery as did the other 6 cases, again developed signs of active inflammation. Repeated courses of penicillin in case 2 produced the same initial response of short duration, followed by relapse.

Because of the large amount of penicillin given initially in case 7, it was not felt that a repeated course would be effective.

In the 6 cases that responded to the specific therapy, clinical recovery occurred in from three to six days, with complete absence of purulent discharge, chemosis and injection.

No corneal complications developed in any of the 8 cases.

As can be seen in cases 1, 3, 4, 5 and 6, occasional gram-negative extracellular diplococci were found on smears taken at varying intervals, even though cultures remained negative and the eyes were clinically normal. No further treatment was given and these cases were kept under observation until three consecutive negative smears and cultures were obtained.

Because of the persistence of clinical activity in case 2, treatment was continued despite the three consecutive negative smears and cultures obtained early in the period of observation, and later both smears and cultures were again found positive.

The treatment progress of each case is outlined in table 1.

Bacteriologic Response.—Smears and cultures were taken in all cases before beginning therapy, at the time of the third injection of penicillin and at intervals thereafter until the bacteriologic criteria of cure as outlined had been fulfilled.

As shown in table 2, all cases except 2 and 8 showed the absence of gram-negative intracellular diplococci in the smears taken at the time of the third injection, although smears in cases 4, 5 and 6 showed the presence of extracellular organisms. Cases 1 and 2 also gave positive cultures at this time, but cultures for all other cases were negative.

Of those cases that responded to penicillin, only 1, case 1, showed a positive culture after the 3d injection of the drug.

Reactions.—A possible reaction to penicillin was observed in case 2. Four days after the second course of penicillin a generalized papular eruption occurred and gradually subsided. Following the third injection of the third course the patient developed a generalized vesicular rash, which subsided during the following ten hours even though penicillin injections were continued. The day after completion of the 3d course a typical urticarial eruption was noted on the trunk and scalp. Although no additional penicillin was administered, the child continued to develop periodic allergic skin manifestations in the form of vesicular, urticarial and pustular lesions.

SUMMARY

1. Eight cases of ophthalmia neonatorum were treated with intramuscular injections of penicillin in total dosages varying from 60,000 to 330,000 units.

2. In 5 of the 8 cases the etiologic agent was definitely established as Neisseria gonorrhoeae by confirmatory fermentation tests; in 2 of the cases gram-negative intracellular diplococci gave positive oxidase reactions when grown on chocolate agar but could not be subcultured for confirmatory fermentation tests; in 1 case the infective agent could not be determined.

3. Six of the 8 cases responded promptly to penicillin with pronounced clinical improvement within twenty-four hours and complete recovery within three to six days.

4. The disappearance of specific organisms in smears and cultures was noted in from nine to twenty-four hours after beginning treatment with penicillin.

notes

A METHOD OF PROLONGING THE ACTION OF PENICILLIN[1]

THE clinical effectiveness of penicillin has been well established. However, from the standpoint of determining optimum dose, period of time necessary for treatment and of inconvenience both to patient and personnel, present methods[2, 3, 4, 5, 6] of administration are not completely satisfactory.

In this study a method of administration of penicillin is reported which decreases the rate of absorption, prolongs the duration of an effective level in the blood and is of minimum inconvenience to the patient.

Beeswax has been used to prolong the action of histamine,[7] desoxycorticosterone acetate[8] and heparin.[9]

Prior to the utilization of beeswax, in February, 1944, we had suspended penicillin in refined peanut oil, sesame oil, cottonseed oil, castor oil and protamine zinc in an attempt to produce prolonged action in rabbits after intramuscular injections. More enduring levels resulted than occur with penicillin in physiological saline, but a greater prolongation was desirable.

Under sterile conditions, 0.75 per cent., 1.0 per cent., 1.25 per cent., 2.0 per cent., 3.0 per cent., 4.0 per cent., 5.0 per cent. and 6.0 per cent. mixtures of U.S.P. bleached beeswax in peanut oil were prepared. Two to 3 cc of the clear warmed beeswax-peanut oil mixture were added with a warm pipette to an ampule of penicillin which had previously been shaken by hand to break the penicillin into as powdery a state as possible. Three to 5 sterile glass beads were then placed in the bottle which was stoppered and shaken by hand for ten to fifteen minutes until the particles of penicillin were well dispersed.

Stability tests[10] on the penicillin in oil and in beeswax-peanut oil mixture show no deterioration in various batches kept at refrigerator, room and 37 degrees C. temperature for 30 to 62 days.

As initial experiments rabbits were injected intramuscularly with 5,000 to 10,000 Oxford units of penicillin contained in 1 cc of beeswax-peanut oil mixture and blood assays[11] were made. Whereas penicillin in saline maintained a level for only two hours, penicillin

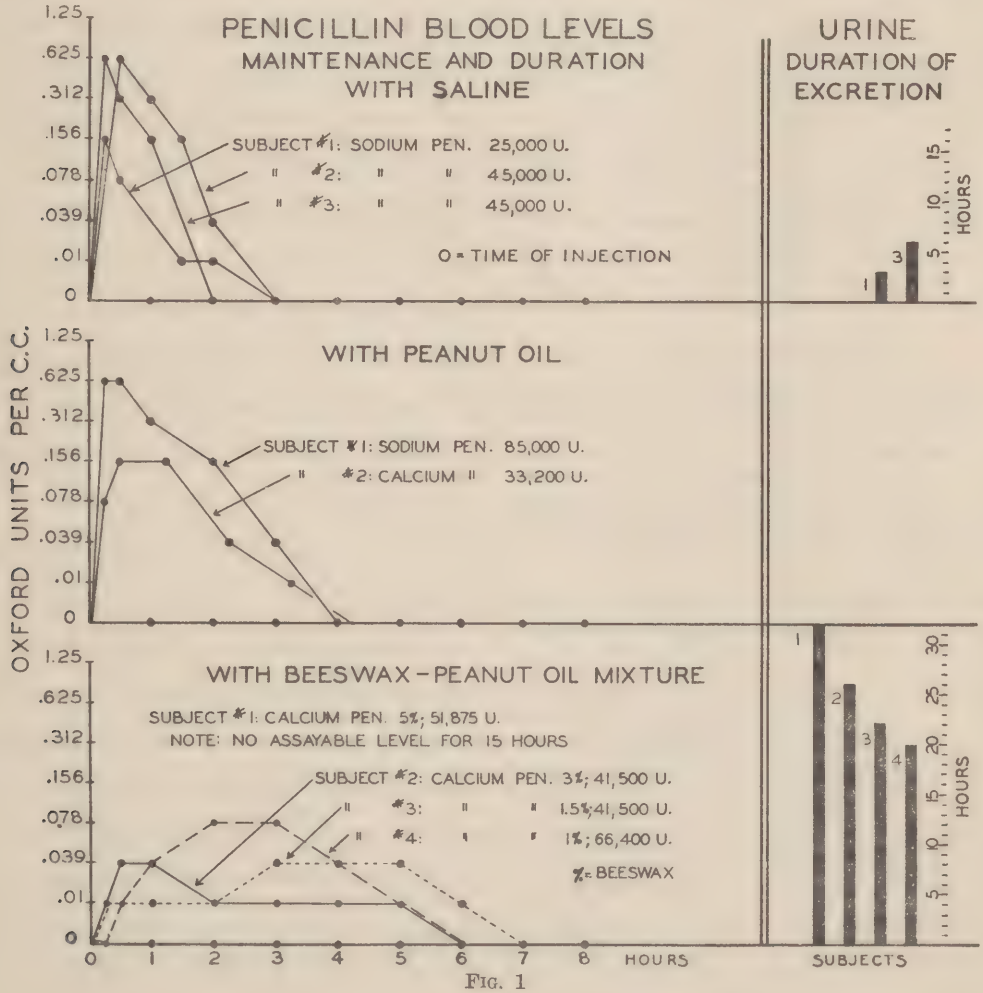

FIG. 1

[1] From the Penicillin Section, Laboratory Service, Walter Reed General Hospital. The technical assistance of

in beeswax-peanut oil mixture maintained a level for 6 to 12 hours.

Human subjects were then given single injections of 41,500 to 66,400 Oxford units of penicillin intramuscularly. These doses were contained in 2 to 2.4 cc of beeswax-peanut oil mixtures. The figure shows the maintenance and duration of penicillin levels in the blood obtained by the use of penicillin in saline, peanut oil and the various percentages of beeswax-peanut oil mixtures. The figure also compares the duration of excretion of penicillin in the urine after the injection of penicillin in saline and in beeswax-peanut oil mixture. The beeswax-peanut oil mixture delayed penicillin absorption and maintained a level in the blood for 6 to 7 hours. The presence of penicillin in the urine for 20 to 32 hours indicated a persisting level in the blood for that period of time, though not assayable by present methods.

None of the patients complained of local pain or irritation in the region where the penicillin beeswax-peanut oil mixture had been injected. Nothing suggestive of an allergic reaction occurred in any of the subjects.

Gross and microscopic studies of tissues from hamsters which have been injected with the penicillin beeswax-peanut oil mixture are in process of study.

Eleven of twelve patients[13] with gonococcic urethritis have been cured after receiving a single injection of penicillin beeswax-peanut oil mixture.

The detailed accounts of these investigations will be published in the October, 1944, issue of the *Bulletin* of the U. S. Army Medical Department.

Summary

(1) Single injections of penicillin in beeswax-peanut oil mixture will produce and maintain levels of penicillin in the blood for 7 or more hours.

(2) These mixtures have maintained their potency at room, incubator and refrigerator temperatures for 30 to 62 days and show no signs of deterioration to date.

(3) Eleven of twelve patients with gonorrhoea have been cured by a single injection of penicillin beeswax-peanut oil mixture.[14]

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Miss Dorothy Talbot and Technician (4th grade) Minna Levy is gratefully acknowledged.

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[10] Assays were made by the methods of Rammelkamp[11] and Rake.[12] Penicillin assays of the urine were also done by these methods.

[11] C. H. Rammelkamp, *Proc. Soc. Exp. Biol. and Med.*, 51: 95, October, 1942.

[12] G. Rake and H. Jones, *Proc. Soc. Exp. Biol. and Med.*, 54: 189, 1943.

[13] The cooperation of Captain Robert J. Murphy of the V.D. Ward is appreciated.

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